CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nifedipine retard 30 mg PCH, prolonged release tablets
Nifedipine retard 60 mg PCH, prolonged release tablets

Pharmachemie B.V., Haarlem, the Netherlands

nifedipine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 100102, 100104

21 May 2008

Pharmacotherapeutic group:	Selective calcium channel blockers with mainly vascular effects, Dihydropyridine derivatives
ATC code:	C08CA05
Route of administration:	oral
Therapeutic indication:	Symptomatic treatment of chronic stable angina pectoris as monotherapy or in combination with a beta-blocker. For the treatment of all grades of hypertension.
Prescription status:	prescription only
Date of authorisation in NL:	4 September 2007
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board in the Netherlands (MEB) has granted a marketing authorisation for Nifedipine retard 30 mg PCH and Nifedipine retard 60 mg PCH, prolonged release tablets, from Pharmachemie B.V. The date of authorisation was on 4 September 2007. The product is indicated for symptomatic treatment of chronic stable angina pectoris as monotherapy or in combination with a beta-blocker and for the treatment of all grades of hypertension.

A comprehensive description of the indications and posology is given in the SPC.

Nifedipine is a calcium antagonist and has a spasmolytic effect on the vascular wall of mainly coronary arteries. As a result of the relaxation of arterial muscle, nifedipine reduces peripheral resistance, leading to an improvement of peripheral blood flow whilst decreasing after-load. Therefore, Nifedipine retard PCH is effective in angina pectoris and hypertension.

This application concerns a generic application claiming essential similarity with the innovator products Adalat OROS 30 mg and 60 mg (NL License RVG 14794 and 14795), containing respectively 30 and 60 mg nifedipine, which have been registered in the Netherlands by Bayer B.V. since 24 October 1991.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted five bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the French reference product, Chronadalate LP 30® mg, prolonged release tablet, and British reference product, Adalat LA 60® mg, prolonged release tablet, respectively registered in France and the United Kingdom. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients
The active substance is nifedipine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ph.Eur is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with two additional specifications for residual solvents (methanol and acetone). As the active substance is dissolved during manufacture particle size is not relevant. Certificates of analysis of three production batches have been provided, demonstrating compliance with this specification.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, and the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

The active substance is stable for 5 years when stored in polyethylene bags inside aluminium laminated bags. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

All excipients are usual for oral dosage forms. Talc is usually used as tablet diluent in amounts of 5-30%. Orally ingested it is considered a nontoxic material. Therefore, the somewhat higher amount of talc in this product is considered safe. The amount of the other excipients are usual. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for Eudragit E, denaturated alcohol and ferric oxide red. Eudragit E and denaturated alcohol comply with in-house specifications, and ferric oxide red complies with the specifications laid down in the USP. USP is an official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the USA. The specifications are considered appropriate for adequate quality control.

Medicinal Product

Composition
Nifedipine retard 30 mg PCH and Nifedipine retard 60 mg PCH are round, biconvex tablets with a pale red colour.

The tablets are packed in a carton box with blister strips made of PVC/PVDC and aluminium foil.

The excipients present in the medicinal product are: carbomer, colloidal silicon dioxide (E551), hypromellose (E464), lactose monohydrate, magnesium stearate (E572), methacrylic acid copolymer, macrogol, povidone (E1201), red iron oxide (E172), talc (E533b), titanium dioxide (E171).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The prolonged release formulation has been designed to maintain a pharmacological active level for a long time (about 24 hours) with a once-a-day administration and to reduce the possible side effects caused by the conventional dosage forms. Moreover, the objective was to develop a nifedipine product that would be bioequivalent with the innovator product Adalat OROS 30 mg and 60 mg, prolonged release tablets. The reference products concern the same pharmaceutical form and contain nifedipine in the same amounts. The formulation is a known matrix diffusion system. The tablets are compressed from granules prepared by uniformly distributing the active substance throughout an inert matrix.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 9 production-scale batches (5 batches of 30 mg strength and 4 batches of 60 mg strength) in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for tablets in the Ph.Eur. and includes tests for appearance, identification, assay, average weight, uniformity of weight, dissolution, related substances, residual solvents, identification dyes and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for 4 batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 6 batches of the 30 mg strength and 5 batches of the 60 mg strength in accordance with applicable European guidelines demonstrating the stability of the products over 36 months. The labelled storage conditions are “Store in the original package”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Adalat OROS 30 mg and 60 mg, prolonged release tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of nifedipine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Nifedipine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted five bioequivalence studies in which the pharmacokinetic profile of the test product Nifedipine retard 30 mg and 60 mg PCH) is compared with the pharmacokinetic profile of the French (Chronadalate LP 30® mg) and British reference product (Adalat LA 60® mg).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

Study 1 Single dose study under fasted conditions (30mg tablet)
A randomised, open, single-dose, 2-way cross-over, bioavailability study was carried out under fasted conditions in 24 healthy male subjects, aged 18-45 years. Each subject received a single dose (30 mg) of one of the 2 nifedipine prolonged release tablet formulations. For each subject there were 2 dosing periods, separated by a washout period of 10 days. The tablet was orally administered after a 12 hours fasting period. Blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 36 hours after administration of the products. All subjects were eligible for pharmacokinetic analysis. The bioavailability of the test product Nifedipine retard 30 mg PCH, prolonged release tablet was compared to the French reference product Chronadalate LP 30® mg, prolonged release tablet (Bayer Pharma, France).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nifedipine following single-dose administration under fasted conditions

Treatment	AUC_{0-t}* ng.h/ml	C_{max} ng/ml	t_{max} h	t_{lag} h
Test	319.70 ± 133.58	16.19 ± 7.38	16 (5-36)	2.5 (1.5-3)
Reference	307.50 ± 126.41	16.37 ± 6.14	11 (5-36)	2.5 (1.5-3)
‡Ratio (90% CI)	1.05 (0.90-1.22)	0.96 (0.87-1.08)	--	
CV (%)	30.8%	22.1%	--	

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{lag}	delay between drug administration and the beginning of absorption
t_{max}	time for maximum concentration
‡	ln-transformed values

***** Due to fluctuating values for plasma concentrations at t=36 hours for test and reference substance, no $t_{½}$ and therefore no $AUC_{0-\infty}$ could be calculated.

Based on the pharmacokinetic parameters of nifedipine under fasted conditions, the reference and test tablet are bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 and were comparable with those calculated by the MAH. For reference, as well as for the test, at t=36 hours the plasma concentrations were fluctuating and a good estimation of $AUC_{0-\infty}$ was not possible.

Study 2 Multiple dose study under fasted conditions (30mg tablet)

A randomised, open, multiple-dose, 2-way cross-over, bioavailability study was carried out in 24 healthy subjects (12 male and 12 female), aged 18-45 years. Each subject received one tablet a day for 6 consecutive days of one of the 2 nifedipine prolonged release tablet formulations (30 mg). For each subject there were 2 repeated dosing periods, separated by a washout period of 10 days. Tablets on day 6 were administered with 250 ml water under fasting conditions. Subjects fasted from 12 hours before, until 4 hours after administration. Blood samples were taken predose from day 1 to 6 and at day 6 as well at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 36 hours after administration of the products. All subjects were eligible for pharmacokinetic analysis. The bioavailability of the test product Nifedipine retard 30 mg PCH, prolonged release tablet was compared to the French reference product Chronadalate LP 30® mg, prolonged release tablet (Bayer Pharma, France).

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of nifedipine following multiple-dose administration

Treatment	**AUC_τ** ng.h/ml	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	623.39 ± 373.39	29.94 ± 15.75	15.62 ± 10.42	0.60 ± 0.26
Reference	550.40 ± 291.54	27.60 ± 13.71	16.77 ± 9.01	0.47 ± 0.21
***Ratio (90% CI)**	1.08 (0.98-1.19)	1.07 (0.99-1.15)	0.91 (0.78-1.05)	--
CV (%)	19.5%	15.6%	31.0%	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

Based on the pharmacokinetic parameters of nifedipine under fasted conditions, the reference and test tablet are bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUCτ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 and were comparable with those calculated by the MAH. The C_{min} was within the boundaries of the extended range from 0.75 – 1.33, which is acceptable for this particular active substance with prolonged characteristics. The wide confidence interval for the ratio of C_{min} was caused by the high variability in both test and reference formulations, this was experienced not only on day 6 but throughout steady state. The fluctuation index (PTF) did not differ significantly between test and reference tablet.

Study 3 Single dose, 3-way cross-over study under fasted and fed conditions (30 mg tablet)

A randomised, open, single-dose, 3-way cross-over, 6-sequence, bioavailability study was carried out under fed/fasted conditions in 24 healthy subjects (12 male and 12 female), aged 18-45 years. Each subject received twice a single test tablet either 10 minutes after a high-fat breakfast or after 12 hours of fasting, and one reference tablet was administered 10 minutes after a high-fat breakfast. Each dosing period was separated by a washout period of 10 days. Blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 36 hours after administration of the products. The bioavailability of the test product Nifedipine retard 30 mg PCH, prolonged release tablet was compared to the French reference product Chronadalate LP 30® mg, prolonged release tablet (Bayer Pharma, France).

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nifedipine following single-dose administration

Treatment	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h	MRT h
Test (fasting)	234.21 ± 83.95	11.30 ± 3.52	16 (5-36)	17.64 ± 3.15
Test (fed)	259.32 ± 103.81	15.77 ± 6.78	6 (5-24)	17.12 ± 2.03
Reference (fed)	262.63 ± 91.69	15.08 ± 5.82	6 (5-24)	16.96 ± 2.23
***Ratio (90% CI)** Test(fed) versus test(fasting)	1.135 (0.98-1.32)	1.352 (1.19-1.54)	--	--
***Ratio (90% CI)** Test(fed) versus reference(fed)	0.984 (0.85-1.14)	1.026 (0.90-1.17)	--	--
CV (%)	31.8%	27.3%	--	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
MRT mean residence time
t_{max} time for maximum concentration
***** ln-transformed values

Food increases the rate of absorption and there was a tendency to an increased extent of absorption of nifedipine prolonged release formulations. This corresponded with earlier findings in literature. Regarding the comparison of test and reference, the 90% confidence intervals calculated for C_{max} and AUC_{0-t} after intake of a high-fat breakfast were within the bioequivalence acceptance range of 0.80 – 1.25 and were comparable with those calculated by the MAH. For t_{max} there was no significant difference between test and reference formulation. Based on these results, test and reference tablet are bioequivalent.

Study 4 Multiple dose study under fasted conditions (60 mg tablet)

A randomised, open, multiple-dose, 2-way cross-over, bioavailability study was carried out in 24 healthy male and female subjects, aged 18-45 years. Each subject received one tablet a day for 6 consecutive days of one of the 2 nifedipine prolonged release tablet formulations (60 mg). For each subject there were 2 repeated dosing periods, separated by a washout period of 10 days. Tablets on day 6 were administered with 250 ml water under fasting conditions. Subjects fasted from 12 hours before, until 4 hours after administration. Blood samples were taken predose from day 1 to 6 and at day 6 as well at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 36 hours after administration of the products. All subjects were eligible for pharmacokinetic analysis. The bioavailability of the test product Nifedipine retard 60 mg PCH, prolonged release tablet was compared to the British reference product Adalat LA 60® mg, prolonged release tablet (Bayer, United Kingdom).

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of nifedipine following multiple-dose administration

Treatment	AUC_τ ng.h/ml	C_{max} ng/ml	C_{min} ng/ml	C_{av} ng/ml	PTF% %
Test	1194.04 ± 591.47	59.30 ± 25.12	18.33 ± 10.29	49.75 ± 24.64	0.90 ± 0.37
Reference	1138.42 ± 441.28	55.51 ± 20.86	17.45 ± 8.74	47.43 ± 18.39	0.84 ± 0.32
***Ratio (90% CI)**	1.005 (0.89-1.14)	1.056 (0.94-1.19)	1.007 (0.74-1.37)	--	--
CV (%)	25.47%	24.5%	67.6%	--	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{av} average drug concentration at steady-state
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

Based on the pharmacokinetic parameters of nifedipine, the reference and test tablet are bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC\tau$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 and were comparable with those calculated by the MAH. The C_{min} is outside the range of the extended range from 0.75 – 1.33, this was attributed to the relative high variability of C_{min}. The fluctuation index (PTF) was in line with bioequivalence of test and reference tablet.

Study 5 Single dose, 3-way cross-over study under fasted and fed conditions (60 mg tablet)
A randomised, open, single-dose, 3-way cross-over, 6-sequence, bioavailability study was carried out under fed/fasted conditions in 24 healthy male and female subjects, aged 18-45 years. Each subject received twice a single test tablet either 10 minutes after a high-fat breakfast or after 12 hours of fasting, and one reference tablet was administered after a high-fat breakfast. Each dosing period was separated by a washout period of 7 days. Blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 36 hours after administration of the products. The bioavailability of the test product Nifedipine retard 60 mg PCH, prolonged release tablet was compared to the British reference product Adalat LA 60® mg, prolonged release tablet (Bayer, United Kingdom).

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nifedipine

Treatment	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{lag} h	MRT h
Test (fasting)	595.94 ± 223.08	30.49 ± 9.61	5.5 (4-36)	2.5 (1-3)	19.38 ± 2.57
Test (fed)	725.65 ± 298.04	39.30 ± 15.96	7 (3-24)	2.5 (0.5-4)	17.12 ± 2.70
Reference (fed)	760.73 ± 330.2	40.51 ± 15.90	6 (5-24)	2 (1.5-4)	17.15 ± 1.61
***Ratio (90% CI)** Test(fed) versus test(fasting)	1.196 (1.07-1.34)	1.240 (1.10-1.39)	--	--	--
***Ratio (90% CI)** Test(fed) versus reference(fed)	0.950 (0.85-1.07)	0.949 (0.85-1.07)	--	--	--
CV (%)	24.3%	24.3%	--	--	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
MRT mean residence time
t_{lag} delay between drug administration and the beginning of absorption
t_{max} time for maximum concentration
***** ln-transformed values

Food increases the rate and extent of absorption of nifedipine prolonged release formulations, as was expected from literature. Regarding test and reference, the 90% confidence intervals calculated for C_{max} and AUC_{0-t} are within the bioequivalence acceptance range of 0.80 – 1.25 and were comparable with those calculated by the MAH. There was no significant difference between test and reference formulation for t_{max} after intake of a high- fat breakfast. However, the confidence interval of the t_{max} was within the boundaries of the extended range from 0.75 – 1.33. This is acceptable for this particular active substance with prolonged characteristics. Based on these results, test and reference tablet are bioequivalent.

Conclusion

A single dose study was performed only for the 30 mg nifedipine formulations. The 90% confidence intervals calculated for the 30 mg tablets for AUC_{0-t} and C_{max} were in agreement with those calculated by the MAH and within the acceptance range of 0.80 – 1.25.

The multiple dose studies in fasting conditions showed for both strengths that 90% confidence intervals of the pharmacokinetic parameters AUC_{τ} and C_{max} were within the acceptance range of 0.80 – 1.25. A large variability in both test and reference nifedipine plasma-levels was observed, especially for C_{min}. A comparable extent of variability in C_{min} was observed throughout steady state for both test and reference tablets.

In a 3-way food interaction study for both the test and reference 30 mg and 60 mg strengths under non-fasting conditions, the 90% confidence intervals calculated for AUC_{0-t} and C_{max} were within the acceptance range of 0.80 – 1.25. Pharmacokinetic parameters, C_{max} and AUC_{0-t}, for test tablets administered under fed conditions versus test tablets taken under fasting conditions were not bioequivalent. Tablets taken with food had a faster rate and slightly increased extent of absorption. This corresponds with earlier findings in the literature.

Based on the pharmacokinetic parameters of nifedipine, it can be concluded that the test tablet (Nifedipine retard 30 mg PCH and Nifedipine retard 60 mg PCH) and the reference tablet (Chronadalate LP 30® mg, Bayer Pharma, France and Adalat LA 60® mg, Bayer, UK) are considered bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The content of the SPC approved during the national procedure is in accordance with the outcome of the article 29(2) of the Directive 2001/83/EC referral procedure for Nifedipine Pharmamatch retard 30 mg and Nifedipine Pharmamatch retard 60 mg (NL/H/0607/01-02) decided on by the European Commission on 26 January 2006. The referral was initiated by the United Kingdom, because of differences between the SPCs of the reference product and the generic product regarding contraindications in women capable of child bearing and nursing mothers.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nifedipine retard 30 mg PCH, prolonged release tablets and Nifedipine retard 60 mg PCH, prolonged release tablets have a proven chemical-pharmaceutical quality and are generic forms of Adalat OROS® 30 mg and 60 mg, prolonged release tablets. Adalat OROS is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The SPC is in accordance with the outcome of the article 29(2) of the Directive 2001/83/EC referral procedure for Nifedipine Pharmamatch retard 30 mg and Nifedipine Pharmamatch retard 60 mg (NL/H/0607/01-02) decided on by the European Commission on 26 January 2006.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Nifedipine retard 30 mg PCH and Nifedipine retard 60 mg PCH, prolonged release tablets with the reference product, and has therefore granted a marketing authorisation on 4 September 2007.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 4 September 2007 till 4 September 2010.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of procedure	Approval /non approval	Assessment report attached
Change to batch release arrangements of the finished product.	type IA no. 8b1	7-9-07	13-11-07	Y	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product.	type IA no. 7b1 met consequential type IA no. 7a	7-9-07	15-11-07	Y	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product.	type IA no. 7b1 met consequential type IA no. 7a	7-9-07	19-11-07	Y	N