Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedures

Felodipine/Delofine XL 2.5 mg, 5 mg and 10 mg Prolonged-Release Tablets

(felodipine)

Product Licence Numbers:
PL 20117/0397-0399

Morningside Healthcare Limited

LAY SUMMARY

Felodipine/Delofine XL 2.5 mg, 5 mg and 10 mg Prolonged-Release Tablets

(felodipine)

This is a summary of the Public Assessment Report (PAR) for Felodipine/Delofine XL 2.5 mg, 5 mg and 10 mg Prolonged-Release Tablets. It explains how these products were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Felodipine/Delofine tablets in this lay summary for ease of reading.

For practical information about using Felodipine/Delofine tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Felodipine/Delofine tablets and what are they used for?
These applications are for generic medicines. This means that this medicine is the same as, and considered interchangeable with reference medicines already authorised in the European Union (EU) called Plendil 2.5 mg, 5 mg and 10 mg prolonged-release tablets (AstraZeneca UK Ltd).

Felodipine/Delofine tablets are used in the treatment of high blood pressure (hypertension) and heart and chest pain brought on by for example exercise or stress (angina pectoris).

How do Felodipine/Delofine tablets work?
Felodipine/Delofine tablets contain the active substance felodipine, which belongs to a group of medicines called calcium antagonists. This medicine lowers blood pressure by dilating small blood vessels. It does not negatively affect the heart function.

How are Felodipine/Delofine tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

Felodipine/Delofine tablets should be taken in the morning without food or following a light meal not high in fat or carbohydrates. The tablet should be swallowed with water and must not be divided, crushed or chewed.

Hypertension
Treatment should be started with 5 mg once a day. If necessary, a doctor may increase the dose or add another blood-pressure lowering medicine. The usual dose when treating this disease for a long time is 5-10 mg once a day. In elderly patients, a starting dose of 2.5 mg daily may be considered.

Stable angina pectoris
Treatment should be started with 5 mg once a day and if needed, a doctor may increase the dose to 10 mg once a day.

If patient have liver problems, the level of felodipine in the blood may be increased. A doctor may lower the dose.

Elderly people
A doctor may initiate treatment with the lowest available dose.

For further information on how Felodipine/Delofine tablets are used, please refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Felodipine/Delofine tablets have been shown in studies?
Because Felodipine/Delofine tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Felodipine/Delofine tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Felodipine/Delofine tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Felodipine/Delofine tablets approved?
It was concluded that, Felodipine/Delofine tablets have been shown to be comparable to and bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Felodipine/Delofine tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Felodipine/Delofine tablets The RMP details the important risks of Felodipine/Delofine tablets, how these risks can be minimised, any uncertainties about Felodipine/Delofine tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Felodipine/Delofine tablets.

The information included in the SmPCs and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by

healthcare professionals and patients. Side effects of Felodipine/Delofine tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

A (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Felodipine/Delofine tablets
Marketing Authorisations for Felodipine/Delofine tablets were granted in the United Kingdom (UK) on 04 January 2022.

The full PAR for Felodipine/Delofine tablets follows this summary.

This summary was last updated in March 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Felodipine/Delofine XL 2.5 mg, 5 mg and 10 mg Prolonged-Release Tablets (PL 20117/0397-0399) could be approved.

The products are approved for the following indications:

- Hypertension
- Stable angina pectoris

Felodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing systemic vascular resistance. Due to the high degree of selectivity for smooth muscle in the arterioles, felodipine in therapeutic doses has no direct effect on cardiac contractility or conduction. Because there is no effect on venous smooth muscle or adrenergic vasomotor control, felodipine is not associated with orthostatic hypotension.

Felodipine possesses a mild natriuretic/diuretic effect and fluid retention does not occur.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Plendil 2.5 mg, 5 mg and 10 mg prolonged-release tablets (AstraZeneca UK Ltd), that have been licensed within the UK for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence studies were conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) on 04 January 2022.

II QUALITY ASPECTS

II.1 Introduction

These products are prolonged release tablets. Each tablet contains 2.5 mg, 5 mg or 10 mg felodipine as an active substance.

In addition to felodipine, these products also contain the excipients hydroxypropylcellulose (E463), hypromellose (E464), lactose monohydrate, macrogolglycerol hydroxystearate, aluminium magnesium silicate, sodium stearyl fumarate making up the tablet core. The tablet coat consists of hypromellose (E464), titanium dioxide (E171), macrogol and yellow iron oxide (E172).

The finished products are packaged in polyvinylchloride (PVC)/polyethylene (PE)/polyvinyldichloride (PVdC)/aluminium blister in packs of 14, 20, 28, 30, 50, 90, 98 and 100 tablets are available.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

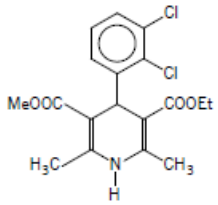
II.2 ACTIVE SUBSTANCE

rINN: Felodipine

Chemical Name: Ethyl methyl ((4RS)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate
3,5-Pyridinedicarboxilic acid 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-,ethylmethyl ester,(±)-
(±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Molecular Formula: $C_{18}H_{19}CL_2NO_4$

Chemical Structure:



Molecular Weight: 384.3 g/mol

Appearance: A white or light crystalline powder.

Solubility: Practically insoluble in water, freely soluble in acetone, in ethanol, in methanol and in methylene chloride.

Felodipine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process have been validated and have shown satisfactory results.

Finished Product Specification
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years with no special temperature storage conditions is approved.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of felodipine are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of felodipine is well known. With the exception of data from four bioequivalence studies, no new clinical data are provided or are required for this type of applications. An overview based on a literature review and a review of these studies are, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of these applications, the Applicant submitted the following four bioequivalence studies:

Study 1
This is an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study of Felodipine 10 mg Prolonged-Release Tablets with Modip® Retardtabletten Felodipin (AstraZeneca GmbH) in healthy, adult, male, human subjects under fasting condition.

Subjects were administered with the test or the reference product.

Blood samples were collected before dosing and up to and including 96 hours after drug administration. The study periods were separated by a wash-out period of 7 days**.**

A summary of the pharmacokinetic results are presented below:

Parameter	Geometric LSM Ref	Geometric LSM test	Ratio(%)	ISCV (%)	Power (%)	Lower 90% CI	Upper 90% CI
LnC_{max} (ng/ml)	6.576	7.288	110.82	35.711	98.78	100.90	121.72
$LnAUC_{0-t}$ (mg.hr/ml)	93.701	81.292	86.76	25.252	99.99	81.11	92.80
$LnAUC_{0-\alpha}$ (ng.hr/ml)	101.486	88.836	87.53	24.338	99.99	82.03	93.41

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

Study 2
This is an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study of Felodipine 10 mg Prolonged-Release Tablets with Modip® 10 mg Retardtabletten Felodipin (AstraZeneca GmbH) in healthy, adult, male, human subjects under fed condition.

Subject were given a high-fat, high calorie breakfast. Subjects were administered with the test or the reference product.

Blood samples were collected before dosing and up to and including 96 hours after drug administration. The study periods were separated by a wash-out period of 7 days.

A summary of the pharmacokinetic results are presented below:

Parameter	Geometric LSM test	Geometric LSM ref	Ratio(%)	ISCV (%)	Power (%)	Lower 90% CI	Upper 90% CI
LnC_{max} (ng/ml)	14395.90	15201.97	94.70	36.51	91.99	84.92	105.60
$LnAUC_{0-t}$ (mg.hr/ml)	104431.05	105906.63	98.61	21.92	99.97	92.24	105.41
$LnAUC_{0-\alpha}$(ng.hr/ml)	110658.67	112356.14	98.49	22.16	99.96	92.07	105.36

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

Study 3
This is an open-label, balanced, randomized, multiple-dose, two-treatment, two-sequence, two-period, full replicate crossover bioequivalence study of Felodipine 10 mg Prolonged- Release Tablets with Modip® 10 mg Retardtabletten Felodipin (AstraZeneca GmbH) in healthy, adult, male, human Subjects under fasting condition with two consecutive-day profiling of Test or Reference product at steady-state in each period.

Subjects were administered with the test or the reference product.

Blood samples were collected before dosing and up to and including 23.92 hours after drug administration. The study periods were separated by a wash-out period of 10 days.

A summary of the pharmacokinetic results are presented below:

Parameter	Geometric LSM test	Geometric LSM ref	Ratio(%)	ISCV (%)	Power (%)	Lower 90% CI	Upper 90% CI
$LnC_{max,\ ss}$	8702.01	7502.32	115.99	21.58	99.98	108.28	124.25
$LnC\tau,ss$	1943.61	2151.62	90.33	23.69	99.91	83.78	97.40
$LnAUC\tau,ss$	89887.35	89610.15	100.31	14.89	100	95.63	105.21

The 90% CI of $C_{max,ss}$, $C_{\tau,ss}$ $AUC_{0-\tau}$, ratios were within the conventional 80.00% - 125.00% range. In general, the results support the bioequivalence of the test formulation with the

reference product, in line with the current CHMP guidelines EMA/CHMP/EWP/280/96Rev1 and CHMP/EWP/QWP/1401/98 Rev.1/Corr**.

Study 4

This is an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, four-period, full replicate crossover bioequivalence study of Felodipine 2.5 mg Prolonged-Release Tablets with Plendil® retard 2.5 mg Filmtabletten Felodipin (AstraZeneca Osterreich GmbH) in healthy, adult, male, human Subjects under fasting condition.

Subjects were administered with the test or the reference product.

Blood samples were collected before dosing and up to and including 96 hours after drug administration. The study periods were separated by a wash-out period of 7 days.

A summary of the pharmacokinetic results are presented below:

Parameter	Geometric LSM ref	Geometric LSM test	Ratio (%)	ISCV (%)	S_{wr}	Widened acceptance criteria	Observe 90%	Power
$LnC_{max,}$ (pg/ml)	1376.00	1550.83	112.71	30.83	0.32769	77.95-128.28	103.66-122.54	99.66

Parameter	Geometric LSM ref	Geometric LSM test	Ratio (%)	ISCV (%)	Power (%)	Observe 90% Cl
$LnAUC_{0-t}$ (pg.hr/ml)	19571.88	20746.49	106.00	28.82	99.86	98.00-114.65
$LnAUC_{0-\alpha}$ (pg.hr/ml)	21250.20	22656.69	106.62	28.87	99.86	98.56-115.34

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength of the products (5 mg and 2.5 mg strength (single dose fed and multiple dose studies) meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence studies on the 2.5 mg and 10 mg product strengths can be extrapolated to the other strength (5 mg and 2.5 mg strength (single dose fed and multiple dose studies).

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

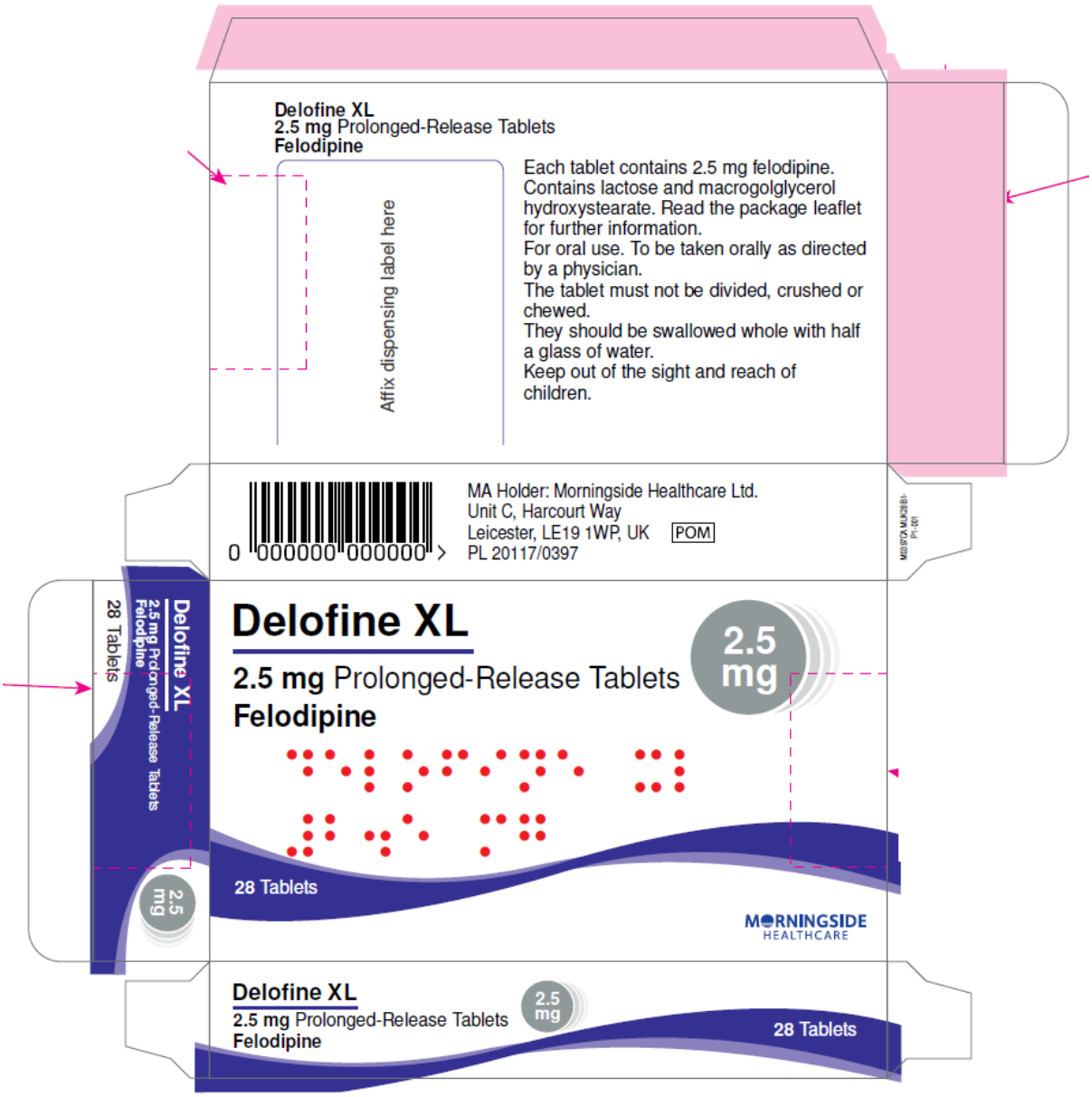
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with felodipine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Delofine XL
2.5 mg Prolonged-Release Tablets
Felodipine
Affix dispensing label here
Each tablet contains 2.5 mg felodipine.
Contains lactose and macrogolglycerol hydroxystearate. Read the package leaflet for further information.
For oral use. To be taken orally as directed by a physician.
The tablet must not be divided, crushed or chewed.
They should be swallowed whole with half a glass of water.
Keep out of the sight and reach of children.
0 000000 000000
MA Holder: Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
POM
PL 20117/0397
Delofine XL
2.5 mg Prolonged-Release Tablets
Felodipine
28 Tablets
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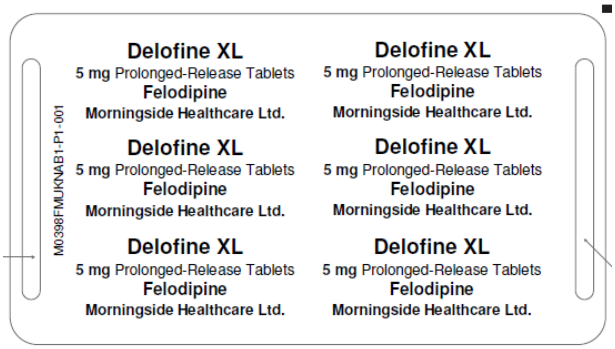
28 Tablets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Felodipine
28 Tablets


Delofine XL
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Felodipine
Morningside Healthcare Ltd.
M0399-FMUKNA B1- P1-001


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For oral use. To be taken orally as directed by a physician.
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Felodipine
10 mg
28 Tablets

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**