23 October 2014
EMA/707004/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

Plendil and associated names

INN of the active substance: Felodipine

Marketing authorisation holder: AstraZeneca group of companies and associated companies

Procedure no: EMEA/H/A-30/1385

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the procedure

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

On 12 November 2013 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

Plendil 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 November 2013 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Alar Irs (EE) as rapporteur and Martina Weise (DE) as co-rapporteur.

Plendil medicinal products are registered in the following European Union (EU) Members States (MS): Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden and United Kingdom and also in Iceland and Norway.

Plendil medicinal products are currently not registered in the following EU MS: Slovenia.

2. Scientific discussion during the referral procedure

2.1. Introduction

Felodipine is a dihydropyridine-type calcium channel blocker (calcium antagonist) and is indicated for the control of hypertension and in many countries also for the treatment of stable angina pectoris.

Plendil was originally approved for marketing in Denmark in 1987, as an immediate release tablet. This formulation was available until 1994, though only launched in Australia. Today, Plendil is available worldwide for oral administration as a prolonged release tablet (except in Japan where another immediate release tablet is marketed). In Europe, the prolonged release tablet was first approved in December 1987 and was first launched in Denmark in 1988. The prolonged release tablet is available in three tablet strengths 2.5mg, 5mg and 10mg.

Plendil has been approved through national procedures in the following countries in EEA: Austria, Belgium , Bulgaria , Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia , Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden and the United Kingdom.

Three European procedures have been completed leading to agreed wording in Plendil SmPCs:

- UK/W/002/pdWS/001 Article 45 Paediatric Workshare, finalised 15 October 2009.
- SK/H/PSUR/0006/001, PSUR (01 Jan 2007 to 31 Dec 2009), finalised 20 October 2011 with agreed Core Safety Profile (CSP).
- SK/H/PSUR/0006/002, PSUR (01 Jan 2010 to 31 Dec 2012), finalised 4 December 2013 and where no changes to the Product Information were proposed.

Due to the divergent national decisions taken by MS concerning the authorisation of Plendil and its associated names, these products were included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, requested by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh). The European Commission notified the European Medicines Agency/ Committee for Medicinal Products for Human Use (EMA/CHMP) secretariat of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised product information (PI) for the above-mentioned products and thus to harmonise them across the EU. A pre-referral meeting between the EMA and marketing authorisation holder (MAH) was held on 14 October 2013. The CHMP addressed a list of questions to the MAH, pointing out the sections of the products SmPC where divergences existed.

2.2. Critical Evaluation

The CHMP endorsed the MAH proposal to harmonise Plendil SmPC having in consideration a "chronological build" of relevant current information from the completed European Procedures and labelling variations as mentioned above and thereafter:

- The agreed Core Safety Profile (CSP) for felodipine prolonged release tables dated 20 October 2011 as baseline text (SK/H/PSUR/0006/001 and SK/H/PSUR/0006/002).
- Wording from Article 45 Paediatric Workshare procedure UK/W/002/pdWS/001 in Plendil SmPC section 5.1 and 5.2.
- The company Core Data Sheet (cCDS), dated 24 October 2012.
- Editorial changes to align the Product Information text with the current QRD template (Version 9, 03/2013).

Section 4.1 – Therapeutic Indications

The CHMP requested the MAH to clarify the divergences in the section 4.1 of the SmPC. The divergences were observed in both indications:

- hypertension;
- stable angina pectoris.

The wording for hypertension was divergent in all EU MSs. The CHMP endorsed the MAH proposal of having *"Hypertension"* as the wording for this indication.

For the indication *"Stable angina pectoris"*, there were several divergences across MSs. The different MSs had "stable angina pectoris and vasospastic angina (variant of Prinzmetal's angina)", "Prophylaxis of angina pectoris (stable and vasospastic forms)", "Angina pectoris" and "Stable exertional angina pectoris; Plendil can be given as monotherapy or can be combined with a beta blocker. Plendil can also be used in the treatment of vasospastic (Prinzmetal's) angina".

The MAH proposed not to include the indication "vasospastic angina" in the harmonised SmPC. The CHMP asked the MAH to further discuss the totality of available data on felodipine and dihydropyridine calcium channel blockers to support the indication of vasospastic angina, since currently calcium channel blockers are in prominent position for this indication.

Vasospastic angina pectoris (also known as variant angina or Prinzmetal angina), is a condition of acute attacks of myocardial ischaemia provoked by focal temporary spasms in subepicardial coronary arteries, associated with spontaneously resolving ST-segment elevations in the electrocardiography

(ECG), and without indications of myocardial injury. The mechanisms underlying the spasms have not been fully elucidated, but involve multiple pathways for activating smooth muscle contractions. The MAH provided data on three clinical studies on vasospastic angina pectoris:

- Study V520 – randomised double blind single dose cross-over trial of immediate release felodipine 10 mg vs. placebo in 14 male patients, selected on basis of anginasymptoms associated with transient ST-segment elevations of ≥0.1 mV, and a positive hyperventilation test (performed ≥ 24 hours after cessation of nitrate and Ca^{2+}-channel blocker therapy) showing ST-segment elevation.
- Study V532+V532LT – blinded 6 days cross-over trial of extended release felodipine, 10 mg and 20 mg 4 times daily vs. placebo 4 times daily. Upon completion of the blinded part, the patients continued in an open part with felodipine 20 mg once daily (could after 6 months be reduced to 10 mg once daily in asymptomatic patients). Included patients displayed reversible ≥ 0.1 mV ECG ST-segment elevations in association with chest pain attacks, a positive ECG reaction to ergonovine or hyperventilation provocation. Prior to starting study medication, ongoing therapy was ceased over 48h. This was followed by a run-in period of two days. The patients were then randomised to one of the treatment arms. No wash-out occurred between the 6 day treatment periods.
- Study V544 – study in 14 patients (2 women) with a history of chest pain at rest, transient ST-segment elevation of ≥0.1 mV, and a positive ergonovine test. Four patients were free of coronary arterystenoses at coronary angiography. After a washout period of 2-7 days coronary angiography was performed (no ergonovine provocation was conducted). Two days later intravenous ergonovine was administered, after which felodipine extended release 20 mg o.d. was started and continued for at least 5 days. Four and 24 hours after felodipine repeat ergonovine provocation was carried out.

The results of the conducted studies on felodipine in vasospastic angina show an effect on the condition, as there are improvements in angina symptoms and reductions or disappearance of transient ST-segment elevations at hyperventilation or systemic ergonovine provocation. However, outside the referenced trials, no significant publication have been found, limiting the total reported material on felodipine use in vasospastic angina to around 30 patients. The total published experience of felodipine in vasospastic angina pectoris and the accumulated safety information is too limited to define a robust benefit risk ratio. Data on the efficacy and safety of specifically felodipine in this indication are very scarce and the MAH did not discuss the extrapolability of the results obtained with other dihydropyridines in this indication. Consequently, the CHMP agreed with the MAH that, although vasospastic angina indication is a condition where the current European Society of Cardiology (ESC) clinical guidelines recommend calcium channel blockers like felodipine as the first-line treatment, an indication for vasospastic angina pectoris cannot be justified.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.2 – Posology and method of administration

Posology

Hypertension

The MAH provided data on a recent multifactorial double blind prospective placebo controlled randomised clinical trial, the study D4386C00013 on mild to moderate hypertension that included 3

arms of Plendil ER (2.5 mg, 10 mg, and 20 mg). While blood pressure was progressively reduced by increments in dose, the 20 mg dose was associated with a higher incidence of adverse events which for peripheral vascular reactions and heart rate were out of proportion to what was seen for the other two doses, relative to placebo. Hence, the CHMP endorsed the MAH proposal on the maximum dose to be 10 mg once daily.

The CHMP also requested down titration from 5 mg starting dose to 2.5 mg in hypertension, depending on the patient's response.

Angina pectoris

The wording on "Angina pectoris" was divergent, since five MSs did not have Angina pectoris as an indication, this wording was missing. Other SmPCs MSs had deviations from the CSP on maintenance dose (10 mg daily), splitting of dose in two, doses up to 20 mg/day, starting treatment with 5 mg, indication in left ventricular impairment, in the absence of any clinical signs of decompensation (except in the case of recent myocardial infarction) and regarding the use in combination with β-blockers, ACE inhibitors or diuretics. The CHMP endorsed the MAH proposal of keeping the CSP text as the harmonised SmPC across EU MSs.

Elderly population

The wording on elderly population was within the same meaning in all MSs, although four MSs expanded the CSP text by adding *"The recommended initial dose is 2.5 mg felodipine. Particular care should be taken when increasing the dose."* and one MS had *"In the elderly population, the maximum dose of felodipine is 5 mg daily".* The CHMP endorsed the MAH proposal of keeping the CSP text as the harmonised SmPC across EU MSs.

Renal impairment

Renal impairment wording was missing in the SmPCs of three MSs. In the SmPCs of four MSs there were the following wording:*"Special care is necessary in patients with severe renal impairment."* The CHMP endorsed the MAH proposal of keeping the CSP text as the harmonised SmPC across EU MSs.

Hepatic impairment

In the SmPCs of two MSs the wording was missing. The SmPCs of four MSs mentioned that felodipine was contraindicated in patients with severe liver impairment, one MS had that the recommended dose was 2.5 mg once daily, other MS recommended 5 mg once daily and one MS had mentioned that 2.5 mg in patients with impaired liver function might be sufficient and that doses higher than 10 mg would not be needed. The CHMP endorsed the MAH proposal of keeping the CSP text as the harmonised SmPC across EU MSs.

Paediatric population

The wording in section 4.2 regarding paediatric population was divergent. The CHMP endorsed the MAH proposal of keeping the CSP text as the harmonised SmPC across EU MSs.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.3 – Contraindications

The CHMP asked the MAH to comment on the following: stroke in the past 6 months, Hypertrophic cardiomyopathy, Atrioventricular block grade 2 and 3, Severe renal impairment (GFR<30ml/min, creatinine >1.8 mg/dl), Severe hepatic impairment/liver cirrhosis, Breast-feeding women/breast feeding infants, Treatment with calcium channel blockers.

- Stroke in the past 6 months

Hypertension is a major risk factor for stroke, and it is well recognised that low high blood pressure will result in reductions in cerebrovascular events. Furthermore, recent and comprehensive evaluations on the use of calcium channel blockers in hypertensive patients with stroke do not indicate a detrimental effect (Mancia 2013, Chen 2013). Consequently, the CHMP agreed with the MAH in its proposal not to have "Stroke within the past 6 months" as a contraindication;

- Hypertrophic cardiomyopathy

Adverse effects from felodipine in hypertrophic cardiomyopathy are limited to those patients with outflow obstruction. Consequently, the CHMP endorsed the MAH position of not including "Hypertrophic cardiomyopathy" among contraindications in the EU harmonised SmPC;

- Atrioventricular block grade 2 and 3

Felodipine, when used in therapeutic doses, has no effect on atrio-ventricular conduction (Amlie et al 1990, Jones et al 1985, Carruthers, Bailey 1987). The CHMP agreed with the MAH position of not including "Atrioventricular block grade 2 or 3" among the contraindications for Plendil in the EU harmonised SmPC;

- Severe renal impairment

The CHMP agreed with the MAH position of not including 'Severe renal impairment' to the contraindications section of the EU harmonised SmPC for Plendil;

- Severe hepatic impairment/liver cirrhosis

Felodipine is cleared in the liver by cytochrome P450 3A4. The potential need for dose adjustments in patients with impaired liver function is addressed in section 4.2 and section 4.4 of the harmonised SmPC for felodipine. The CHMP agreed with the MAH position of not including "Severe hepatic impairment/liver cirrhosis" as a contraindication in the EU harmonised SmPC for felodipine, since it is appropriately covered in sections 4.2 and 4.4 of the agreed SmPC for Plendil;

- Breast-feeding women/breast feeding infants

As mentioned in section 4.6, felodipine is detected in breast milk. However, the data available do not indicate that felodipine in breast milk will have an effect on breastfed infant. The CHMP agreed with the MAH position of not including "Breast-feeding women/ breast feeding infants" as a contraindication in the EU harmonised SmPC for Plendil;

- Treatment with calcium channel blockers

While the MAH recognises that the combination of Plendil with another calcium channel blocker is an unlikely combination, the proposed harmonised SmPC gives the prescriber the necessary information for a considerate use. The CHMP agreed with the MAH position of not including "Treatment with calcium channel blockers" as a contraindication in the EU harmonised SmPC for Plendil.

The CHMP accepted the proposal from the MAH to adopt the contraindications: pregnancy; Hypersensitivity to felodipine or any of the excipients listed in section 6.1; decompensated heart failure, instead of uncompensated heart failure as previously; acute myocardial infarction; unstable angina pectoris; haemodynamically significant cardiac valvular obstruction and dynamic cardiac outflow obstruction as the harmonised text.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.4 – Special warnings and precautions for use

Divergences were found in section 4.4 of the SmPC. Some MSs were missing text from the CSP and some MSs had different text.

Considering that gingival enlargement is a known adverse reaction to treatment with felodipine and it is preventable by good oral hygiene, the CHMP endorsed the MAH proposal on including mild gingival enlargement has been reported in patients with pronounced gingivitis/peridontitis in the section 4.4 of the harmonised EU SmPC for Plendil.

The use in combination with potent inhibitors or inducers of CYP3A4 is more appropriately addressed in sections 4.5 and 5.2 of the MAH proposal for a harmonised EU SmPC for Plendil. The CHMP therefore considered it necessary to include the following text in Section 4.4, including a reference to Section 4.5:

'Concomitant administration of drugs that strongly induce or inhibit CYP3 A4 enzymes result in extensively decreased or increased plasma levels of felodipine, respectively. Therefore such combinations should be avoided (see section 4.5).'

A warning that *'The efficacy and safety of felodipine in the treatment of hypertensive emergencies has not been studied'* was also included.

Finally the CHMP requested the MAH to add a warning on castor oil. The information on castor oil is given under section 2 and section 6 of the proposed harmonised SmPC text. The MAH is of the opinion that castor oil is an excipient in Plendil tablets in an amount too small to have any effects, except for possibly hypersensitivity and hypersensitivity to any component of the product is a contraindication. The MAH agreed and included that 'Plendil contains castor oil, which can cause stomach upset and diarrhoea'.

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

The wording was divergent for this section across EU SmPCs. The MAH made a proposal in line with the agreed CSP wording, with one addition and one deletion as per CDS. The CHMP asked the MAH to insert statements regarding interactions leading to increased plasma concentrations of felodipine and interactions leading to decreased plasma concentrations of felodipine. These changes were agreed by the CHMP , leading to the wording below:

(…) 'Interactions leading to increased plasma concentration of felodipine

CYP3A4 enzyme inhibitors have been shown to cause an increase in felodipine plasma concentrations. Felodipine Cmax and AUC increased 8-fold and 6-fold, respectively, when felodipine was coadministered with the strong CYP3A4 inhibitor itraconazole. When felodipine and erythromycin were coadministered, the Cmax and AUC of felodipine were increased by about 2.5-fold. Cimetidine increased the felodipine Cmax and AUC by approximately 55%. The combination with strong CYP3A4 inhibitors should be avoided.

In case of clinically significant adverse events due to elevated felodipine exposure when combined with strong CYP3A4 inhibitors, adjustment of felodipine dose and/or discontinuation of the CYP3A4 inhibitor should be considered. (…)

Felodipine tablets should not be taken together with grapefruit juice.

Interactions leading to decreased plasma concentration of felodipine

Enzyme inducers of the cytochrome P450 3A4 system have been shown to cause a decrease in plasma concentrations of felodipine. When felodipine was coadministered with carbamazepine, phenytoin or phenobarbital, the Cmax and AUC of felodipine were decreased by 82% and 96% respectively. The combination with strong CYP3A4 inducers should be avoided.

In case of lack of efficacy due to decreased felodipine exposure when combined with potent inducers of CYP3A4, adjustment of felodipine dose and/or discontinuation of the CYP3A4 inducer should be considered.'

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.6 – Fertility, pregnancy and lactation

The wording in section 4.6 was divergent.

The MAH provided the CHMP with the justification of the reason why "Reproductive toxicity studies have demonstrated foetotoxicity effects" should not be in the harmonised EU SmPC for Plendil. The findings in the reproduction studies do not demonstrate evidence of direct fetotoxicity. The MAH considers that the fetodevelopmental findings in the rabbit, and the consequences of the prolonged parturition in the rat, are due to the pharmacological action of felodipine. The MAH agreed to include *"In non-clinical reproductive toxicity studies there were a foetal developmental effects, which are considered to be due to the pharmacological action of felodipine."*

Pregnancy

Regarding the sentence *"Pregnancy must be excluded before starting treatment with felodipine/ suitable contraceptive measure should be taken to prevent pregnancy"*, the MAH safety surveillance for Plendil has not identified adverse effects of fertility or pregnancy related nature to be excessive or increasing. Furthermore, during the initial weeks of pregnancy the embryo is nourished by the yolk sack, and, consequently, not exposed to felodipine taken by the mother to be. Subjective recognition of pregnancy usually occurs at the end of this period. It is expected that the patient has been informed to seek medical advice in that situation, and that all aspects of therapies are considered, including actions to be taken regarding discontinuation of felodipine treatment. The CHMP endorsed the MAH position not to include *"Pregnancy must be excluded before starting treatment with felodipine/suitable contraceptive measure should be taken to prevent pregnancy"* in section 4.6 of the harmonised EU SmPC for Plendil.

The final agreed wording is as follows*: 'Felodipine should not be given during pregnancy. In non-clinical reproductive toxicity studies there were foetal developmental effects, which are considered to be due to the pharmacological action of felodipine'.*

Lactation

The initial proposal from the MAH for the EU harmonised wording on Breastfeeding was "*Felodipine is detected in breast milk. When taken in therapeutic doses by the nursing mother it is, however, not likely to affect the infant*". The CHMP asked the MAH to further substantiate this sentence, or in case of data are not available, to add that breastfeeding during treatment with felodipine is not recommended given the lack of data. The MAH reworded the text accordingly with CHMP requests *"Felodipine has been detected in breast milk, and due to insufficient data on potential effect on the infant, treatment is not recommended during breastfeeding"*.

Fertility

The following wording was agreed:

There are no data on the effects of felodipine on patient fertility. In a nonclinical reproductive study in the rat (see section 5.3), there were effects on fetal development but no effect on fertility at doses approximating to therapeutic.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.7 – Effects on ability to drive and use machines

The CHMP proposed an alternative text in line with amlodipine harmonised SmPC for this section:
"Felodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking felodipine suffer from headache, nausea, dizziness or fatigue the ability to react may be impaired. Caution is recommended especially at the start of treatment."
The MAH agreed with the above proposed wording.

Section 4.8 – Undesirable effects

The proposal for the harmonised EU SmPC is based on the CPS from 2011 and CDS from October 2012. Modifications relate to deletion of unnecessary and outdated wording, table format and addition of hypotension as an ADR.

The MAH justified the deletion of ADRs using the Empirical Bayesian Data Mining techniques to compute disproportionality scores from the MAH's global safety database. This method generates the Empirical Bayesian Geometric Mean (EBGM) with a 90% confidence interval (EB05 to EB95). The MAH considered an EB05 > 1.8 a possible signal i.e. the event is reported disproportional often in association with that drug. Searches were also conducted in the FDA Adverse Event Reporting System (AERS) database and in the WHO Vigibase database. Overall, the statement of grounds for not including adverse events included in one or few national texts was considered acceptable by the CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.9 – Overdose

The CHMP endorsed the MAH proposal on a minor re-wording of section 4.9 of the CSP and to implement it as the harmonised text across EU MS. The CHMP requested the MAH to add information on when a gastric lavage should be performed.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 5.1 – Pharmacodynamic properties

The CHMP requested the MAH to shorten the text related to pharmacodynamic properties since it included parts of limited clinical relevance or not considered justified by clinical evidence. The MAH agreed to remove the parts suggested by the CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 5.2 – Pharmacokinetic properties

The wording on section 5.2 was divergent across MSs. Some MSs were missing a text referring to absorption, distribution, metabolism and elimination. The CHMP endorsed the MAH opinion on adopting the CDS text with some modifications, since it covers the pharmacokinetic properties of felodipine.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 5.3 – Preclinical safety data

The MAH proposed the use of section 5.3 of the CDS for the preclinical section of the harmonised EU SmPC for felodipine, since the text is based on current non clinical nomenclature. The CHMP requested that this section reflect that data showed abnormal position of the distal phalanges in offspring of monkeys. The MAH included the information regarding the preclinical data, and subsequent text to state that it cannot be stated with certainty that the pharmacological effects are not relevant for humans.

'There were no other pre-clinical findings considered to be of concern and the reproductive findings are considered to be related to the pharmacological action of felodipine, when given to normotensive animals. The relevance of these findings for patients receiving felopidine is unknown. However, there have been no reported clinical incidences of phalangeal changes in foetus/neonate exposed to felodipine in-utero, from the information maintained within the internal patient safety databases.'

Package Leaflet (PL)

Following all the changes in the SmPC there were amendments made to the Package Leaflet. The final PL wording was agreed by the CHMP. Please see Product Information for Plendil and associated names in Annex III.

2.3. Risk Management Plan

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

2.4. Recommendation

In conclusion, the CHMP recommended the revision and harmonisation of the Product Information for Plendil and adopted the following harmonised indications:

Plendil is indicated for the:

- hypertension;
- stable angina pectoris.

2.5. Conclusions

Based on the assessment of the MAH proposal and responses and following the discussions of the Committee, the CHMP adopted harmonised sets of Product Information documents of Plendil and associated names.

Whereas

- the scope of the referral was the harmonisation of the Summary of Products Characteristics, labelling and package leaflet,
- the Summary of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

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