Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Overall summary of the scientific evaluation of Plendil and associated names (see Annex I)

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 on 16 March 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 the European Economic Area (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 Summary of Product Characteristics (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 Member States (MS) concerning the authorisation of Plendil and its associated names, these products were included in the list of products for 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.

It is hereafter summarised the main points discussed for the harmonisation of the different sections of the SmPC.

Section 4.1 – Therapeutic Indications

Plendil is indicated for:

- 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. 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. 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 agrees with the MAH that, although vasospastic angina indication is a condition where the current European Society of Cardiology clinical guidelines recommend calcium channel blockers like felodipine as the first-line treatment, an indication for vasospastic angina pectoris cannot be justified.

Section 4.2 – Posology and method of administration

The section 4.2 was divergent across MSs. The divergences were due to differences in the indication, recommendation in maximum daily dose and down titration. There were also discrepancies regarding recommendations for special population groups namely elderly and paediatric, renal and hepatic impairment, administration with/ without food.

The CHMP endorses the MAH proposal in adopting the CPS text as the harmonised text, deleting text that is not present in the referred document.

Section 4.3 – Contraindications

Divergences were found in section 4.3 of the SmPC.

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

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.

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 the warning "mild gingival enlargement has been reported in patients with pronounced gingivitis/periodontitis" 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 considers 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).'

Besides a warning that 'The efficacy and safety of felodipine in the treatment of hypertensive emergencies has not been studied' was also be included in view of the missing evidence with felodipine in hypertensive emergencies and to be in agreement with the product information of amlodipine the Rapporteurs see the need to include the warning as proposed in the LoOI.

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 and 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

For the section 4.5, the MAH proposed to use the text from the CSP, with one addition and one deletion as per CDS. The wording was divergent for this section across EU SmPCs. The CHMP asked the MAH to insert statements regarding interactions leading increased plasma concentration of felodipine and interactions leading to decreased plasma concentration of felodipine. These changes were agreed accordingly.

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, included 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, 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.

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 wording on section 4.8 was divergent. 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 adverse drug reaction (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 is considered acceptable by the CHMP.

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.

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.

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.

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 some additional wordings. The MAH included the information regarding the preclinical data, and subsequent text added to state that it cannot be stated with certainty that the pharmacological effects are not relevant for humans.

Grounds for the variation to the terms of the marketing authorisations

In conclusion, 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).