Annex II

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

Scientific conclusions

Overall summary of the scientific evaluation of nicardipine-containing products for intravenous use (see Annex I)

Nicardipine is a calcium channel blocker of the dihydropyridine type which is primarily effective via peripheral vasodilatation in vascular smooth muscle rather than cardiac muscle. Following the submission of a marketing authorisation application under the decentralised procedure (DCP) for a generic nicardipine-containing product for intravenous (IV) use (10 mg/10ml solution for injection) and the assessment of the application dossier, the reference member state (RMS) UK considered the clinical data submitted to be insufficient to determine the efficacy, safety and overall benefit-risk of IV nicardipine in the proposed indications. No bioequivalence is required for intravenous generic products and no such data was therefore submitted. In addition, significant discrepancies between the information submitted and the posology and safety information in the proposed Summary of product characteristics (SmPC) were also identified by the RMS.

The RMS therefore decided to suspend the DCP procedure at day 210 and triggered a procedure under Article 31 of Directive 2001/83/EC, requesting the Committee for Medicinal Products for Human Use (CHMP) to review the benefit-risk of all intravenous nicardipine-containing products for intravenous use and to clarify the data supporting the licensing of these products. In view of the identified divergences in the nationally approved product information, the CHMP also considered it to be of community interest to harmonise the product information across the EU.

The CHMP considered all data available in its assessment, including published studies, article and guideline reviews, expert statements, user surveys, national guidelines as well as safety data from post-marketing and marketing authorisation holder databases.

The CHMP considered that overall, sufficient evidence is available on the safety and efficacy of nicardipine containing medical products for IV use in the treatment of post-operative hypertension and treatment of acute life-threatening hypertension in specific settings, with appropriate specialist intervention and monitoring and when used by specialists. The CHMP considered that there is a role for intravenous nicardipine in aortic dissection based on the information submitted, the evidence of widespread use, the expert statements and the absence of new safety signals in this patient population; however, in line with the available evidence, the CHMP recommended the clinical use as second line treatment, when short acting beta-blocker therapy is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective. Intravenous nicardipine can also continue to be used in malignant arterial hypertension/hypertensive encephalopathy; however, due to the risk of intracranial pressure elevation, the CHMP recommended the addition of a warning on this risk. Regarding the treatment of severe hypertension in pregnancy, the CHMP took into account the limited study data, the lack of long-term study data on morbidity and mortality and the recommendations of current guidelines. Despite being used as a first line treatment in some member states, the CHMP considered a second-line indication to be appropriate for IV nicardipine for pre-eclampsia and agreed on an indication in severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated.

In view of the available evidence and current medical knowledge on the use of intravenous nicardipine, and considering the potentially serious adverse reactions associated with the use of nicardipine, the CHMP considered that the benefit-risk balance of IV nicardipine is negative in some indications due to serious limitations of the efficacy data.

There are safety concerns associated with the use of nicardipine in patients with left ventricular heart failure as well as in patients with suspected coronary artery disease and therefore nicardipine should no longer be used for acute severe hypertension with accompanying left ventricular decompensation and pulmonary oedema. With regards to hypotension, the CHMP considered that the use of intravenous nicardipine for this indication is no longer relevant in the context of current surgical and anaesthetic practice. Considering the limited efficacy data and overall safety profile, the CHMP therefore considered that the indications in hypotension should be removed from the product information.

The CHMP reviewed the broad indication for hypertension in the peri-operative period, which includes the pre-operative phase, the time of surgery itself and the post-operative period. The CHMP concluded that data is only available to support the use of nicardipine in the post-operative hypertension indication setting.

The CHMP also made significant revisions to the posology section of the product information, including bringing the recommendations in special populations in line with current knowledge of the use of intravenous nicardipine. Having reviewed the available safety data, the CHMP noted that most common

adverse effects and those that most frequently result in drug discontinuance are cardiovascular and nervous system effects related to the expected vasodilator effects of the drug, in particular headache, hypotension, flushing, oedema and tachycardia. Gastrointestinal intolerance such as nausea also occurs. These adverse effects are consistent with other dihydropyridine calcium channel blockers and were not considered to impact negatively on the benefit-risk balance of IV nicardipine. Additionally, significant concerns were raised regarding the administration of IV nicardipine by bolus dose injection or direct intravenous administration due to a higher potential risk of iatrogenic hypotension, in particular in pre-eclampsia. No suitable risk minimisation measures were identified to reduce the associated risks, given the nature of the patient population and the possible emergency setting in which IV nicardipine is used. The CHMP therefore concluded that nicardipine for intravenous use should only be administered by continuous infusion and not by bolus dose administration, due to the above-mentioned safety concerns.

Overall conclusion and benefit –risk balance

The Committee, as a consequence, concluded that the benefit-risk balance of intravenous nicardipine-containing medicinal products remains positive, taking into account the restrictions, warnings and other changes to the product information.

Grounds for the variation to the terms of the marketing authorisation

Whereas

- The Committee reviewed all available data, including the responses submitted by the marketing authorisation holders, published studies and post-marketing data;
- The Committee considered that the available efficacy data is supportive of the use of nicardipine for intravenous use in the treatment of acute life-threatening hypertension and post-operative hypertension;
- The Committee considered that in view of the identified serious limitations of the efficacy data and the overall safety profile of nicardipine, the benefits were no longer considered to outweigh the risks for some indications, which should therefore be removed;
- The Committee considered that the product information should be updated, including with regard to the therapeutic indications and advised that nicardipine should only be administered by continuous infusion and not by bolus dose administration, due to safety concerns.

The Committee, as a consequence, concluded that the benefit-risk balance of nicardipine-containing medicinal products for intravenous use remains positive under normal conditions of use, taking into account the changes to the product information agreed.