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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nicardipine-containing medicinal products for intravenous use

INN/active substance: nicardipine

Procedure number: EMEA/H/A-31/1339

Referral under Article 31 of Directive 2001/83/EC

Note

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



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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 17 July 2012, the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for nicardipine-containing medicinal products for intravenous use and associated names should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

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. A marketing authorisation application under the decentralised procedure (DCP) was submitted for a generic nicardipine-containing product for intravenous (IV) use (10 mg/ 10ml solution for injection), making reference to the French product Loxen. No intravenous nicardipine product had ever been licensed in the UK and following 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, the posology and safety information proposed in the DCP application and the information of the nationally-approved product information 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 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.

2.2. Clinical efficacy

Having reviewed the MAHs responses, the CHMP noted the divergences in indications and posology between the various nicardipine-containing products. Notably, use in severe hypertension with left ventricular failure, in aortic dissection, or in some anaesthetic settings was not approved for some products. Some summaries of product characteristics (SmPCs) did not provide a posology for children, and whilst some gave a recommendation for bolus IV dosing, others specifically warned that nicardipine should not be administered directly as an IV injection. There were also significant inconsistencies in the advice relating to use in patients with renal impairment. The CHMP considered all data available for review. Only relevant information is discussed hereinafter.

Severe hypertension

The CHMP reviewed the available efficacy data on IV nicardipine in the treatment of acute severe hypertension, in particular review articles by Cherney (2002), Curran (2006), Chobonian (2003), Varon (2008), Rhoney (2009), Van der Born (2010) and Marik (2011), together with study publications by Wallin (1989), Yang (2004), Hwang (2012), Peacock (2011), Malesker (2012), Neutel (1994), Kim (2002), Tao (1998) and Escande (1989). The CHMP only considered results in patients with end-organ damage to be of relevance to the proposed indications and noted that there were differences between the studies in terms of the patient populations and the posology used and that information was missing in some. Some studies were uncontrolled and not all studies provided data on adverse events.

Based on the data made available by the MAHs, the CHMP considered that overall, nicardipine appears to be effective as an infusion within the proposed dosing range in acute severe hypertension, with some comparative data to both nitroprusside and labetalol. In the study by Peacock (2011), in the subgroup of patients with severe hypertension also defined as having end-organ damage at presentation, 91.4% patients receiving IV nicardipine were within prospectively defined target blood pressure range within 30 minutes, compared to 76.1% of those treated with IV labetalol. The Neutel study suggested comparable efficacy of IV nicardipine within the proposed posology to nitroprusside in patients with severe hypertension, and that nicardipine was better tolerated than nitroprusside.

Dose titration appeared to be manageable, with no adverse rate of “overshoot” in relation to the compared treatments, which would otherwise result in iatrogenic hypotension and contribute to increased morbidity risk. The recent Dutch national guidelines on the management of hypertensive crisis were also noted in which nicardipine is suggested as a treatment option for hypertensive crisis associated with hypertensive retinopathy or stroke, particularly if labetalol is contraindicated.

The CHMP however raised some concerns regarding use in severe hypertension in patients with heart failure, as only a single, small open-label study using a posology slightly different to that proposed in the SmPC is available. This indication is also not endorsed in any submitted national guidelines. The setting of severe hypertension with consequent acute heart failure is sufficiently different from the treatment of severe hypertension in other settings to require separate assessment. Calcium channel blockers can have negative inotropic effects while dihydropyridines have a positive chronotropic effect.

The CHMP also reviewed data from a study by Kumada (1995) on the use of nicardipine in the treatment of heart failure, but considered that this indication was significantly different from the indication of relevance “hypertensive crisis with secondary heart failure” and that patient morbidity, concomitant medication and physiological environment would therefore differ. The study also used a different infusion regimen to the infusion posology proposed in the IV nicardipine SmPC under discussion. A further Japanese study by Hirota (1997) of nicardipine in the treatment of acute heart failure was considered as not relevant to the proposed indications. A number of other studies involving nicardipine in the treatment of heart failure were also discussed by the MAHs but these used a different posology and were not considered to support the indication. The CHMP also noted that the 2012 European Society of Cardiology heart failure guidelines do not mention nicardipine, stating instead that intravenous nitrates or nitroprusside are recommended to lower blood pressure.

In conclusion, the CHMP considered that 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 that intravenous nicardipine should therefore no longer be used for *acute severe hypertension with accompanying left ventricular decompensation and pulmonary oedema*.

In the setting of aortic dissection, an uncontrolled study by Kim demonstrated that IV nicardipine was effective in controlling blood pressure in patients with acute aortic dissection, while a publication by Peacock (2001) and the Dutch guidelines suggested that calcium channel blockers are not recommended as first-line agents in the setting of aortic dissection, beta-blockers having a potential physiological advantage in this setting. In addition, a retrospective review of antihypertensive therapy in the intensive care unit by Malesker (2012) makes no specific mention of use in aortic dissection. The short evidence-based review by Wong (2011) concludes that randomised controlled trials are needed to clarify the effectiveness and safety of nicardipine in the treatment of hypertensive emergency in acute aortic dissection. Concerns were raised over the potential reflex tachycardia associated with calcium channel blockers.

A Korean clinical study in 2002 by Kim including 31 patients showed that nicardipine initiated at an infusion rate of approximately 2 mg/h and titrated to a maximum of 30mg/h via central venous catheter was effective in controlling blood pressure in patients with acute aortic dissection confirmed by CT scan. The CHMP however noted that the study was uncontrolled with short follow-up and that patients taking oral beta-blockers were allowed to continue taking them simultaneously with nicardipine, and that the authors commented that this combination was desirable.

The CHMP noted that review articles suggest that nicardipine has a role as a vasodilator option in aortic dissection and that most state that this should be in combination with a beta-blocker only or that nicardipine is a second line treatment only when beta-blockers are not effective.

The CHMP was of the view that based on the information submitted, the evidence of use, the expert statements and the absence of new safety signals, the use in severe acute hypertension with aortic dissection could be considered acceptable, provided that the SmPC reflects 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. The CHMP consequently adopted the following indication:

"Aortic dissection, when short acting beta-blocker therapy is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective".

Having concluded that the general use of IV nicardipine in acute severe hypertension for acute medical conditions is adequately supported by data, the CHMP was of the view that malignant arterial hypertension with stage III hypertensive retinopathy and hypertensive encephalopathy could be considered as examples of end-organ damage, given that the indications are in life-threatening, severe hypertension with associated organ damage. The CHMP reviewed the available data, including a double-blind, placebo-controlled multicentre trial by Wallin (1989) which involved 123 patients with severe hypertension and a similar study by Peacock (2011) in acute severe hypertension with end organ damage. The CHMP also noted that the use of nicardipine in these patients is endorsed in the Dutch guidelines. With regards to severe retinopathy, only a very small number of patients were included in the studies, and the CHMP noted safety concerns such as increased risk of bleeding.

The CHMP noted that according to a French survey, malignant hypertension represents 11% of the total prescription of IV nicardipine in France. Globally, 60% of the interviewed clinicians claim the use of nicardipine as a first line treatment (up to 90% for cardiologists and 80% for ICU specialists and nephrologists). Similar statistics were obtained for the hypertensive encephalopathy indication (8% of the total prescriptions for IV nicardipine).

Having assessed the data, the CHMP considered that whilst data is limited, results show that nicardipine may cause intracranial pressure elevation and may therefore not be a first-line choice in patients with pre-existing elevated intracranial pressure (see also discussion in the safety section of this report). The CHMP therefore considered this indication to be acceptable, provided that an adequate warning regarding the effect on intracranial pressure is added to the product information. In conclusion, the CHMP adopted the following indication:

"Malignant arterial hypertension/Hypertensive encephalopathy"

Together with the following warning:

"Patients with pre-existing elevated intracranial pressure

Intracranial pressure should be monitored, to allow calculation of the cerebral perfusion pressure."

Treatment of severe hypertension in pregnancy

The CHMP reviewed the available data on the use of IV nicardipine in the treatment of severe hypertension in pregnancy. A number of guidelines were reviewed, including a review of the Dutch guidelines, a Cochrane review of drugs for treatment of very high blood pressure during pregnancy by Duley (2006), the UK NICE guidelines (2010) on the treatment of hypertensive disorders during pregnancy and the European Society of Hypertension / European Society of Cardiology guidelines (2003) on the management of arterial hypertension. The CHMP also reviewed five studies of nicardipine in acute hypertension of pregnancy, by Aya (1999), Hanff (2005), Carbonne (1993), Seki (2002) and Elatrous (2002), including a total of 147 patients. The studies by Aya and Hanff were small, uncontrolled observational studies comprising a total of 47 patients. IV nicardipine was generally well tolerated by the mother with adequate efficacy in controlling blood pressure; however the data was limited, with short follow-up and the dose regimens varied. Only one randomised controlled study (Elatrous, 2002) was identified in which IV nicardipine was comparable to IV labetalol, with 30 patients per group and without long-term follow-up. IV nicardipine was comparable to IV labetalol in terms of time to blood pressure goal. Both drugs were apparently well tolerated except for tachycardia observed with nicardipine. Other maternal side effects in the nicardipine group included nausea and palpitations. The paper notes that foetal tolerance was generally good, apart from one transient heart rate deceleration in a labetalol patient. Overall, nicardipine was generally well tolerated by the mother, however the lack of extensive controlled data limits interpretation. The CHMP also reviewed a review article by Vadhera (2009) on the use of nicardipine in pregnancy, which concludes that based on limited clinical data, nicardipine may be considered when other antihypertensive medications have failed to achieve blood pressure control. No evidence of an increased risk of postpartum haemorrhage secondary to uterine atony was identified. According to guidelines published by the French societies of anaesthesiology, gynaecology and neonatology, IV nicardipine is a first-choice treatment, at the same level as labetalol in the treatment of pre-eclampsia. A further retrospective descriptive study by Monia (2012), conducted during 2009-2010 in a Tunisian centre and involving 150 patients with severe pre-eclampsia was also reviewed. Data on clinical experience on the use of nicardipine for life-threatening pre-eclampsia was noted, particularly in France, with a 2010 French publication considering it a first-line treatment. However, the CHMP also noted that the Dutch guidelines position nicardipine in a second-line role in pre-eclampsia, when labetalol is contraindicated or does not lower blood pressure sufficiently.

Taking into account the limited study data, the lack of long-term study data on morbidity and mortality, the recommendations of current guidelines and the safety concerns for mothers, the CHMP considered a second-line indication to be appropriate for IV nicardipine for pre-eclampsia. The CHMP therefore agreed on the following indication:

"Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated"

The CHMP also revised and harmonised the posology section accordingly, introducing a more conservative dose regimen. Given the risks of maternal hypotension and the identified risk of pulmonary oedema, the CHMP agreed on the following precautionary statement to be added as a warning:

"Due to the risk of severe maternal hypotension and potentially fatal foetal hypoxia, the decrease in blood pressure should be progressive and always closely monitored. Due to the possible risk of pulmonary oedema or excessive decrease in blood pressure, caution should be taken if magnesium sulphate is used concomitantly."

Finally, because differences were noted between the various nationally-approved SmPCs with regard to the pregnancy and lactation wording, the CHMP also revised and harmonised the wording of these respective sections.

In this regard, the CHMP took into account the outcome of a review by the Pharmacovigilance Risk Assessment Committee (PRAC). The use of nicardipine for severe pre-eclampsia during the third trimester of pregnancy can potentially produce an undesirable tocolytic effect. Acute pulmonary oedema has been observed when nicardipine has been used as a tocolytic during pregnancy, and the sections on fertility, pregnancy and lactation, together with the undesirable effects, were therefore updated to reflect this information.

Hypotension

There are some studies supporting the use of intravenous nicardipine to achieve controlled hypotension in patients undergoing surgical procedures, including in the spinal surgery setting (Bernard (1992), Hersey (1997), Lustik (2004) and Tobias (1996)) and in the hip arthroplasty setting (Bernard, 1991).

However, the CHMP noted that controlled hypotension is no longer the technique of choice in current clinical practice and proposed to delete the indication, as supported by expert statements according to which controlled hypotension is not used in current anaesthesia practice because of the risk of uncontrolled hypotension. The CHMP considered that the indication is no longer relevant in the context of current surgical and anaesthetic practice, both for adults and children and that the indications in hypotension should be deleted.

Hypertension in the peri-operative period

The proposed indication for hypertension in the peri-operative period was understood to include the pre-operative phase, the time of surgery itself and the post-operative period.

Regarding the post-operative setting, it was noted that nicardipine generally appears to be used by continuous infusion. The CHMP reviewed the data submitted regarding the use of IV nicardipine in the post-operative hypertension setting, including by the IV nicardipine study group (1991), Vincent (1997), Aronson (2008), Goldberg (1990), Madi-Jebara (2002), Halpern (1992) and David (1991). These included several trials comparing nicardipine to placebo in cardiac and non-cardiac surgical patients, and a comparison to IV nitroprusside. Generally, the adverse events mentioned in the studies were consistent with the SmPC and the tolerability was acceptable. There are also a number of studies evaluating repeated bolus doses in the post-operative settings, but no studies compared repeated boluses to a continuous infusion. In the study by Vincent, one patient developed acute pulmonary oedema and myocardial ischaemia following bolus nicardipine administration. The 2008 comparison with clevidipine indicated that the latter was not superior to nicardipine for blood pressure control in the treatment of post-operative hypertension, and showed no difference in 30 day mortality or morbidity. The authors of this trial commented that nicardipine was among the drugs commonly used in the US in a cardiac surgical population. Also, the Dutch guidelines note that nicardipine is favoured over nitroprusside or labetalol for hypertension after cardiac bypass surgery. It states in particular that for coronary bypass surgery, nicardipine appears to have a more favourable effect on maintaining stroke volume and myocardial perfusion than nitroprusside or glyceryl trinitrate. The CHMP concluded that nicardipine is used in the post-operative hypertension indication and that this indication is adequately supported by clinical data, with comparable efficacy to other therapeutic alternatives.

Regarding the broader indication of peri-operative use of nicardipine in hypertension, the CHMP reviewed studies by Kross (2000), Begon (1989) and White (2003) as well as a study by Lien (2012), which states that there is a paucity of literature and accepted guidelines for the peri-operative evaluation and care of patients with hypertension who undergo either cardiac or non-cardiac surgery.

The CHMP was also not convinced that nicardipine is the optimum treatment to prevent a transient spike in blood pressure in this setting, given that its duration of action. The CHMP reviewed the Evaluation of Clevidipine in the Perioperative treatment of hypertension assessing Safety Events (ECLIPSE) study by Aronson (2008), which compared the safety and efficacy of clevidipine with nitroglycerin, sodium nitroprusside and nicardipine in the treatment of peri-operative acute hypertension in patients undergoing cardiac surgery. However, it was noted that the comparison of clevidipine with nicardipine was restricted to the post-operative period.

The CHMP concluded that there is some data for the treatment of other intraoperative severe hypertension, however, the major clevidipine study specifically limited the nicardipine treatment arm to post-operative hypertension only, the authors stating that nicardipine was "not generally used before or during surgery" due to its long half-life and potential for higher serum levels in elderly patients. No new direct comparative data between nicardipine and clevidipine is available. Any increase in heart rate due to nicardipine treatment might negate the benefits of controlling blood pressure during surgery. The Dutch guidelines state that labetalol and nicardipine are equally effective in lowering blood pressure without raising intracranial pressure, but appear to be contradicted by the most recent review by Lien, which considers that nicardipine may cause intracranial pressure elevation and is not a first-line choice in patients with pre-existing elevated intracranial pressure.

Having reviewed all available data on IV nicardipine during surgery, the CHMP was of the view that a number of these studies were small and uncontrolled and that others were not in line with the indication in severe hypertension, with doses generally lower than those proposed in the SmPC. The CHMP considered that the extent of data on IV nicardipine used to control hypertension during surgery remains very limited. In addition, the half-life and duration of action of IV nicardipine are not ideal for use in the context of general anaesthesia, especially in the high-risk surgery for which IV nicardipine might be associated. It is acknowledged that whilst clevidipine has recently been licensed for peri-operative hypertension, some patients have specific contra-indications to it. However, despite any similarity between clevidipine and nicardipine, it is not possible to extrapolate between them, and nicardipine has not yet been compared with clevidipine in intra-operative hypertension. The CHMP was also of the view that peri-operative hypertension may be influenced by changes in anaesthetic techniques, changes in anaesthetic agents, and changes in the assessment and management of blood pressure before surgery. From this viewpoint, pre- and intra-operative use of IV nicardipine is no longer considered to be a relevant indication in the context of current surgical and anaesthetic practice in some member states. Use of a pure vasodilator without first addressing the likely cause of the hypertension poses serious risks to the patient's post-operative outcome. There are many causes of acute intra-operative hypertension, each of which requires appropriate treatment or risk specific complications not corrected by direct vasodilatation. The CHMP therefore considered that the general indication "hypertension during the peri-operative period" should be revised to reflect the accepted indication "treatment of post-operative hypertension".

Posology and method of administration

Regarding the use of IV nicardipine in children, the CHMP reviewed a number of studies in the paediatric population, including studies by Gouyon (1997), Milou (2000), Tenny (2000), Tobias (2001), Flynn (2001), Nakagawa (2004), Treluyer (1993), Thomas (2011) and Michael (1998). Additional review articles by Tobias (2013), Peacock (2012), Chandar (2012), Horn (2011), Eymery (2012), Adelman (2000) and Porto (2000) were also reviewed.

In the submitted studies, nicardipine is claimed to be efficacious and adequately well tolerated in infants and children with severe hypertension, although there are only four prospective studies in children, with no randomised studies against an active comparator (with the exception of a study in adolescents undergoing spinal surgery) and all studies used a different posology from the one stated in the SmPCs. A common theme in the review articles submitted is that for all drug treatments, robust data on safety and efficacy of pharmacological agents in the paediatric population for hypertensive crises are generally lacking, nevertheless, the review articles do indicate appreciable experience of IV nicardipine in children with severe hypertension, particularly in the US and in France.

Other calcium channel blockers are used in paediatric intensive care in the UK, but none are currently licensed for intravenous injection. Although sodium nitroprusside remains one of the most popular drugs for reducing blood pressure in UK paediatric intensive care units, nicardipine is considered to have a favourable comparative benefit-risk balance based on the limited data submitted and IV calcium

channel blockers are considered for use in children in some defined settings, for example following aortic surgery and in life-threatening hypertensive emergencies. Intravenous nicardipine may represent a potentially useful agent in children in certain circumstances. The CHMP recommended an update to the posology to better reflect the available data and guidance in this patient population.

Based on the available data, the CHMP considered that IV nicardipine should only be administered by specialists in well controlled environments, such as hospitals and intensive care units, with continuous monitoring of blood pressure. The recommended starting dose for children was revised to 0.5-5mcg/kg/min across all ages and when a maintenance dosage is required, the recommended dosage is 1 to 4mcg/kg/min. For adults, the optimal initial dosage was determined to be continuous administration at a rate of 3-5 mg/h for 15 minutes. For the maintenance dose, the dosage should be reduced to between 2 and 4 mg/h, to maintain the therapeutic efficacy, with a possible transition to an oral antihypertensive agent.

2.2.1. Discussion on efficacy

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 available to support the use of nicardipine only in the post-operative hypertension 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.

2.3. Clinical safety

The CHMP reviewed all relevant safety data in order to determine the safety profile and benefit-risk balance of IV nicardipine in the proposed indications and to reflect the appropriate information in the SmPC. The CHMP noted several divergences between the proposed and the various nationally-approved SmPCs.

The CHMP reviewed a tabulated overview of safety data collected from a number of clinical trials including studies by the IV nicardipine study group (1991), Nij Bijwank (2010), Kross (2000), Flynn (2001), Tobias (1996), Aya (1999), Cheung (1999), Kovac (2001), Kovac (2007), Gouyon (1997),

Tenney (2000), Milou (2000), Nakagawa (2004), Hanff (2005), Peacock (2011) and Malesker (2012). The studies included adult and paediatric (including preterm infants and neonate) patients with a variety of conditions. The CHMP found that in general, the adverse events observed were reflected in the product information. The quality and detail of the adverse drug reports (ADR) was found to be variable, especially in older studies, and many of the trials were uncontrolled, which severely limits interpretation, given that the setting of use is associated with significant morbidity, underlying serious pathology and the use of multiple concomitant therapies.

The most common adverse effects and those that most frequently result in drug discontinuation 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. Regarding local reactions, these occur mainly in the event of infusion for longer than 16 hours.

The CHMP also reviewed post-marketing data as submitted by the MAHs. Seventeen cases have been reported by one MAH for IV nicardipine, from worldwide sources. Seven case reports were related to local reactions (thrombosis, thrombophlebitis, phlebitis, lymphangitis) which are already described in the product information. A further four unlisted serious case reports included three linked cases of acute pulmonary oedema and one case of dyspnoea. The cases of acute pulmonary oedema were collected from published literature during off-label use as a tocolytic. The remaining six case reports were isolated cases and included lack of efficacy, medication error, headache, hyperhidrosis, chills and tachycardia, and gingival hyperplasia. Data from another MAH on a periodic safety update report covering the period from 1st June 2007 to 31st May 2010, was generally in line with the previous cumulative experience and with the core data sheet. There was one case of severe skin reaction recorded in a patient who received both oral and IV nicardipine, although this was confounded by other medication including amoxicillin/clavulanic acid. The cumulative number of reactions for toxic epidermal necrolysis, Stevens-Johnson syndrome, toxic skin eruption and exfoliative dermatitis as of 31 May 2010 were 5, 2, 11 and 3 respectively according to the post-marketing data.

Eighteen cumulative cases of thrombocytopenia were retrieved from one MAHs' database (for the period up to 31st December 2012). Of these, 14 were serious, of which two had a fatal outcome and four were non serious. Most cases were confounded or alternative explanations were present. For cases where timelines were reported, the event typically occurred within a week of treatment. For cases where drug causality was assumed, recovery was complete after withdrawal of nicardipine or the other potential causal drugs. The outcome in the two fatal cases was secondary to evolution of complications due to underlying condition.

The CHMP noted that the ADR data could not be split by indication and often consisted of pooled oral and intravenous nicardipine data. The CHMP noted the recent periodic safety update reports, including specific signal evaluation reports for paralytic ileus/intestinal obstruction, extrapyramidal syndrome, severe skin reactions (including toxic epidermal necrolysis) and hepatitis.

In conclusion, the CHMP updated the adverse events section of the SmPC, in line with current SmPC guidance and using appropriate frequency terminology, with ADRs separated by SOC and into clinical study and post-marketing reports.

The CHMP reviewed all data on interactions and compared the various nationally-approved SmPC documents. A number of interactions were already in place in some nationally-approved SmPCs, including pharmacodynamic interactions with other medications with antihypertensive or hypertensive effect, PK interactions affecting nicardipine (enzyme inducers, enzyme inhibitors) and PK interactions affecting other products via inhibition of their metabolism. A class warning about co-administration of a calcium channel blocker and dantrolene was also included. The CHMP noted literature on the interaction between nicardipine and inhalational anaesthetics and considered that there is limited and conflicting study data on a potential interaction. Although no signal of clinical concern was identified, a general statement was considered to be warranted in the product information. The issue of the combination with magnesium was also considered relevant to the pre-eclampsia indication. It was noted that some guidelines by the French societies of anaesthesiology, gynaecology and neonatology recommend the combination of IV nicardipine and magnesium sulphate in case of pre-eclampsia with signs of neurologic dysfunction. As the two drugs have a potential pharmacological interaction, the combination with calcium channel blockers should be used with caution and the CHMP therefore considered that a caution statement on concomitant use should be included. Finally, it was noted that intra-operative intravenous nicardipine (as with other calcium channel blockers) can decrease the requirements for vecuronium and other competitive neuromuscular blockers. The CHMP noted that a literature review of interactions with competitive neuromuscular blockers showed controversial results and provided no information concerning any clinical translation of this potential interaction. The neuromuscular blockade routinely requires close monitoring and the reversal of the neuromuscular

block is not affected, nevertheless, the CHMP considered a general statement to be warranted. The CHMP revised the interactions section accordingly and brought it in line with the current SmPC guideline.

The CHMP noted that a number of submitted publications state that nicardipine may cause intracranial pressure elevation and/or is not a first-line choice in patients with pre-existing elevated intracranial pressure. The CHMP therefore reviewed the available data, in particular a prospective case-control study of neurologically critically ill patients by Narotam (2008) which did not find a link between the use of nicardipine and reduced brain oxygen tension and a study by Nishiyama (2000) exploring the long-term effects of nicardipine on cerebral hemodynamics in patients with acute intracerebral haemorrhage and concluding that in these patients, nicardipine infusion decreased blood pressure by 20 to 30%. The CHMP also reviewed a study by Nishikawa et al (1986) investigating the effect of nicardipine on cerebrospinal fluid pressure (CSFP) with 47 patients who were not suffering from any neurologic or cardiopulmonary disorders, concluding that nicardipine may increase CSFP to undesirable levels in patients with intracranial hypertension. A total of seven cases have been reported post-marketing with the preferred terms classified under HLT Increased intracranial pressure disorders. The most reported preferred term was brain oedema (n=5). Four of the seven patients were treated with IV nicardipine, two were treated with oral nicardipine and the formulation in the remaining patient is unknown. Nicardipine was indicated for hypertension (n=4), vasospasm (n=1), premature labour (n=1) and in one case the indication was unknown (n=1). No cases supported a probable relationship between the use of nicardipine and increased intracranial pressure and most cases were confounded by current underlying illness, making a proper assessment of the causal relationship impossible. The CHMP concluded that the available data suggests a possible relationship between the use of nicardipine and the development of increased intracranial pressure disorders and therefore included the following warning in the product information:

"Patients with pre-existing elevated intracranial pressure

Intracranial pressure should be monitored, to allow calculation of the cerebral perfusion pressure."

The CHMP also reviewed the use of bolus administration. While the use of bolus doses by prescribers in some centres was acknowledged, the CHMP noted that in some nationally-approved SmPCs, administration of a bolus dose is specifically advised against, while others provide no posology for bolus injection. The CHMP reviewed the data submitted by the MAHs to support the bolus dose posology, including a pharmacokinetic discussion, additional articles and reference texts, a discussion and survey of medical practice in France and a review of French pharmacovigilance data, as well as expert statements and national guidelines. In particular, the CHMP also reviewed a number of studies of IV nicardipine bolus in acute severe hypertension.

The CHMP noted that some of the data suggested a tendency to prefer continuous infusion over bolus for the treatment of acute severe hypertension, because it is believed safer, more progressive and better controlled, with less risk of severe hypotension. Two small trials were submitted to support the administration of a nicardipine bolus dose in acute severe hypertension. One of these (Escande, 1989) was an uncontrolled study, the other (Tao, 1998) was a comparison of bolus plus infusion vs. infusion. In both these studies, both regimens achieved the therapeutic target, but with the infusion-only regimen clearly better tolerated. No additional support from treatment guidelines or the recent literature was provided. Having reviewed the totality of the data, the CHMP was of the opinion that there is no direct support for the bolus dose in the discussed indication. Data regarding bolus dosing in special populations was even more limited.

The CHMP also noted a proposal from the MAHs to lower the bolus dose, together with additional SmPC cautions and restrictions, however, no convincing data was submitted to support this proposal and the MAHs were unable to properly define the exceptional circumstances, if any, where bolus administration is preferred over a continuous intravenous infusion. The MAHs were also unable to provide clinical data to demonstrate the maximum safe rate of injection and to define patient populations in which this method of administration has been shown to be acceptably safe.

In conclusion, the CHMP was of the view that insufficient clinical data has been presented to compare bolus versus infusion dosing in the same study and no data to show within the same study that more rapid dosing is superior to a slower infusion. Bolus or direct intravenous administration carries a higher potential risk of iatrogenic hypotension, in particular, bolus dosing in pre-eclampsia raises particular safety concerns for both the mother and the unborn baby. The proposal to minimise the risk by restricting bolus use in populations particularly at risk, such as patients with renal impairment was not considered feasible in practice, as a significant percentage of patients requiring IV antihypertensives, particularly in non-surgical settings, will have renal impairment. In addition, in some emergency situations where the patient is presenting a hypertensive crisis, information on renal function will not

immediately be available. The CHMP therefore concluded that nicardipine for intravenous use should not be administered by bolus injection and that reference to bolus or direct intravenous administration is not acceptable, based on the currently submitted data. The SmPC was revised accordingly, together with the inclusion of the following specific warning:

"Bolus administration or intravenous administration not controlled by the use of an electronic syringe driver or a volumetric pump is not recommended and can increase the risk of serious hypotension, particularly in the elderly, in children, in patients with renal or hepatic impairment and in pregnancy".

The CHMP also agreed on specific dosage instructions and recommendations in elderly patients, pregnant women and patients with hepatic impairment. Regarding renal impairment, the CHMP noted that the available data suggested that exposure is clearly higher in renally impaired patients, with a reduction in clearance, including after a single IV dose and the posology was therefore revised accordingly. Regarding paediatric patients, the posology was significantly revised in line with the discussion on the use of IV nicardipine in children. The CHMP included a statement that the safety and efficacy in low birth weight infants, newborns, nursing infants, infants, and children has not been established and that IV nicardipine should only be used for life-threatening hypertension in paediatric intensive care settings or post-operative contexts. The recommended starting dose was revised to 0.5-5mcg/kg/min across all ages and when a maintenance dosage is required, the recommended dosage is 1 to 4mcg/kg/min. The CHMP also considered that particular caution should be exercised when using IV nicardipine in children with renal impairment.

2.3.1. Discussion on safety

Having reviewed the available safety data, the CHMP noted that most common adverse effects and those that most frequently result in treatment discontinuation 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.

2.4. Risk management plan

The CHMP, having considered the data submitted in the application is of the opinion that the following risks (in addition to the established risks already addressed by routine risk minimisation measures, i.e. adequately reflected in the product information) should be addressed in a risk management plan:

- *Cerebral infarction, cerebrovascular accident, cerebrovascular spasm and cerebral syndrome*
- *Paralytic ileus/intestinal obstruction*
- *Toxic epidermal necrolysis, other severe skin reactions*
- *Hepatitis*
- *Overdose*
- *Safety in pregnancy:*
- *Off label use for prevention of premature labour*
- *Reduction of body weight at birth/after birth in the baby*
- *Pulmonary oedema*
- *Peripheral oedema*
- *Hypersensitivity*
- *Extrapyramidal syndrome*
- *Raised intracranial pressure*

- *Off-label use, including bolus administration*

For each risk identified, pharmacovigilance activities and/or risk minimisation measures to address the risk should be proposed. The MAHs should discuss and agree on the implementation plan with the individual national competent authorities. For applicants of products where the MA procedure is not finalised, the RMP should be agreed with the relevant national competent authorities before a marketing authorisation is granted.

2.5. Overall benefit/risk assessment

In its assessment of the benefit-risk balance of IV nicardipine, the CHMP considered all available data, 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 acute life-threatening hypertension, particularly in the event of malignant arterial hypertension/hypertensive encephalopathy; aortic dissection, when short-acting beta blocker therapy is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective; severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contraindicated; and in post-operative hypertension. Appropriate specialist intervention and monitoring and use by specialists is necessary. However, 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 and safety concerns.

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. The CHMP also 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. 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 and were not considered to impact negatively on the benefit-risk balance of IV nicardipine.

The CHMP therefore concluded that the benefit-risk of nicardipine-containing products for intravenous use remains positive under normal conditions of use, subject to the agreed changes to the product information.

2.6. Changes to the product information

The CHMP carried out significant revisions to the product information of nicardipine-containing products for intravenous use, to reflect the available data and clinical experience with IV nicardipine. In particular, the therapeutic indications and the posology and method of administration sections were revised. A number of indications that were inadequately supported by data or no longer of clinical relevance were removed, while some other indications were repositioned as second line indications. In conclusion, the following indications were agreed by the CHMP:

"Intravenous nicardipine is indicated for the treatment of acute life-threatening hypertension, particularly in the event of:

- *Malignant arterial hypertension/Hypertensive encephalopathy*
- *Aortic dissection, when short acting beta-blocker therapy is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective*
- *Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated*

Nicardipine is also indicated for the treatment of post-operative hypertension"

The CHMP also considered that the bolus dose recommendation was not sufficiently justified by data and that IV nicardipine should therefore not be administered as a bolus injection. Changes were also made to the remaining sections of the SmPC and the package leaflet was revised accordingly. Both documents were brought in line with the current product information guidance.

3. Overall conclusion

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.