Public Assessment Report

Decentralised Procedure

NICARDIPINE 10 MG/10 ML SOLUTION FOR INJECTION
(nicardipine hydrochloride)

Procedure No: UK/H/4610/001/DC

UK Licence No: PL 12762/0450

Mercury Pharmaceuticals Limited
This is a summary of the public assessment report (PAR) for Nicardipine 10 mg/10 ml solution for injection (PL 12762/0450). It explains how Nicardipine 10 mg/10 ml solution for injection was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Nicardipine 10 mg/10 ml solution for injection.

For practical information about Nicardipine 10 mg/10 ml solution for injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Nicardipine 10 mg/10 ml solution for injection and what is it used for?

Nicardipine 10 mg/10 ml solution for injection is a ‘generic medicine’. This means that Nicardipine 10 mg/10 ml solution for injection is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Loxen 10mg/ml solution injectable (Novartis Pharma SAS, France).

Nicardipine 10 mg/10 ml solution for injection is prescribed to treat very severe high blood pressure and to control high blood pressure after an operation.

How is Nicardipine 10 mg/10 ml solution for injection used?

This medicine can only be obtained with a prescription. This medicine will be administered by a specialist in a well-controlled environment with continuous monitoring of blood pressure.

How does Nicardipine 10 mg/10 ml solution for injection work?

Nicardipine 10 mg/10 ml solution for injection contains the active ingredient nicardipine hydrochloride. Nicardipine hydrochloride belongs to a group of medicines called calcium channel blockers. Calcium channel blockers affect the way calcium passes into certain muscles, including the heart and the wall of the blood vessels. This causes the muscles to relax and lowers blood pressure.

How has Nicardipine 10 mg/10 ml solution for injection been studied?

This application for Nicardipine 10 mg/10 ml solution for injection is a generic medicine, claiming to be similar to the reference medicine; Loxen 10mg/ml solution injectable (Novartis Pharma SAS, France). Suitable literature reviews and relevant safety data have been reviewed for nicardipine hydrochloride. No new clinical studies were needed or required for this application as Nicardipine 10 mg/10 ml solution for injection is given by injection and contains the same active as the reference product, which is nicardipine hydrochloride.

What are the benefits and risks of Nicardipine 10 mg/10 ml solution for injection?

Nicardipine 10 mg/10 ml solution for injection is a generic medicine and is comparable to the reference medicine, therefore its benefits and risks are taken as being the same as the reference medicine.

Why is Nicardipine 10 mg/10 ml solution for injection approved?

It was concluded that, in accordance with EU requirements, Nicardipine 10 mg/10 ml solution for injection has been shown to have comparable quality and to be comparable to the reference medicine; Loxen 10mg/ml solution injectable (Novartis Pharma SAS, France). Therefore, the view was that, as for Loxen 10mg/ml solution injectable (Novartis Pharma SAS, France) the benefit outweighs the identified
What measures are being taken to ensure the safe and effective use of Nicardipine 10 mg/10 ml solution for injection?

A risk management plan has been developed to ensure that Nicardipine 10 mg/10 ml solution for injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Nicardipine 10 mg/10 ml solution for injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Nicardipine 10 mg/10 ml solution for injection

During the course of the assessment of Nicardipine 10mg/10ml solution for injection, the Committee for Medicinal Products for Human Use (CHMP) were requested to perform an EU-wide assessment on the benefits and risks of intravenous nicardipine products. The CHMP concluded that an intravenous formulation of nicardipine is a useful treatment for high blood pressure in specific hospital settings, and with appropriate specialist intervention and monitoring.

Following the outcome of the review, Belgium and the United Kingdom agreed to grant a Marketing Authorisation for Nicardipine 10 mg/10 ml solution for injection on 18 March 2014. A Marketing Authorisation was granted in the UK on 24 April 2014.

The full PAR for Nicardipine 10 mg/10 ml solution for injection follows this summary. For more information about treatment with Nicardipine 10 mg/10 ml solution for injection, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in June 2014.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Nicardipine 10 mg/10 ml solution for injection (PL 12762/0450; UK/H/4610/001/DC) could be approved.

This application was submitted via the Decentralised Procedure (DCP). On Day 180, the DCP, assessment was suspended and an Article 31 referral under Directive 2001/83/EC was triggered. The Committee for Medicinal Products for Human Use (CHMP) were requested to begin an EU-wide assessment on the benefit-risk balance of intravenous nicardipine products and to issue an opinion to the European Commission (EC) on whether the Marketing Authorisations of intravenous nicardipine products should be maintained, varied, suspended or withdrawn across the European Union.

The CHMP assessment procedure was initiated on 19 July 2012. The CHMP concluded that an intravenous formulation of nicardipine is a useful treatment for high blood pressure in specific settings, and with appropriate specialist intervention and monitoring. The CHMP opinion was sent to the EC, which endorsed it and adopted a final legally binding decision valid throughout EU on 20 December 2013. On 18 March 2014 the United Kingdom (UK) as the Reference member state (RMS) and Belgium (BE) as the Concerned Member State (CMS) adopted the EC decision and approved this application.

This application was made under the Decentralised procedure, according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Loxen 10mg/ml solution injectable (Novartis Pharma SAS), which was granted a Marketing Authorisation in France on 22 June 1988. The UK does not have a suitable, marketed reference product and has accepted the use of the European reference product, and its original data and suitable literature references.

This product can only be obtained with a prescription (legal classification POM). Nicardipine 10 mg/10 ml solution for injection 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

No new non-clinical studies were submitted, which is acceptable given that this application was based on being a generic medicinal product of the reference product Loxen 10mg/ml solution injectable (I.V) that has been licensed for over 10 years.

There are no bioequivalence studies and no new clinical studies submitted for this application. This is acceptable and in compliance with the bioequivalence guidance (CPMP/EWP/QWP/1401/98 Rev. 1/Corr.) which specifies that bioequivalence studies are generally not required if the test product is to be administered as an aqueous solution containing the same active substance as the currently approved reference product. Pharmaceutical equivalence has been shown from the comparative physico-chemical characteristics for the proposed product versus the reference product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 18 March 2014. After a subsequent national phase, a licence was granted in the UK on 24 April 2014.
II QUALITY ASPECTS

II.1 Introduction
Nicardipine 10 mg/10 ml solution for injection is a clear, pale yellow solution. Each ampoule contains 10 mg of Nicardipine hydrochloride in a volume of 10 ml.

Other ingredients consist of the pharmaceutical sorbitol, citric acid monohydrate, sodium citrate, hydrochloric acid, sodium hydroxide and water for injections.

All excipients used comply with their respective European Pharmacopoeia monographs. No genetically modified organisms (GMO) have been used in the preparation of this product. No materials of animal or human origin have been used in manufacture of this product.

The finished product is packed in a type I brown glass ampoule with a One Point Cut (OPC) break system in pack sizes of 5, 10 or 50 ampoules. Not all pack sizes may be marketed.

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

II.2 Drug substance
rINN: Nicardipine hydrochloride
Chemical name: 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic[methyl-(phenylmethyl) amino] ethyl ester hydrochloride acid methyl 2-2-(N-Benzyl-N-methylamino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5 pyridine dicarboxylate hydrochloride (±) – 3 – (2-(N-benzyl-N-methylamino)ethoxy carbonyl)-2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine Hydrochloride

Structure:

![Nicardipine Structure](image)

Molecular formula: C_{26}H_{29}N_{3}O_{6}. HCl
Molecular weight: 515.99
Appearance: pale yellow crystalline powder
Solubility: freely soluble in methanol and acetic acid, sparingly soluble in ethanol and slightly soluble in water, in acetonitrile and acetic anhydride
Synthesis of the active substance from the designated starting material has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate specifications are provided for the active substance nicardipine hydrochloride, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used. Satisfactory specifications have been provided for all packaging used for storing nicardipine hydrochloride. The primary packaging has been shown to comply with current legislation concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable. A suitable retest period has been set based on stability data submitted for the active substance stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to produce a solution for injection containing 10mg/10ml nicardipine hydrochloride that could be considered as a generic medicinal product of the reference product Loxen 10mg/ml solution injectable (Novartis Pharma SAS, France). Comparative physico-chemical characteristics have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed versus the reference product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three commercial-scale batches of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life before opening of 24 months with the storage conditions of “Do not store above 25°C” and “Store in the original container in order to protect from light”. The physico-chemical stability of the undiluted solution or diluted in a solution of 5%
dextrose in water in a polypropylene syringe has been demonstrated for 24 hours at temperatures of +25°C, away from light. However from a microbiological standpoint, the product should be used immediately.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Nicardipine 10 mg/10 ml solution for injection.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The approved labelling is shown below.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of nicardipine hydrochloride are well known. No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
Suitable justification has been provided for the non-submission of an ERA. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Nicardipine 10 mg/10 ml solution for injection.

IV. CLINICAL ASPECTS

IV.1 Introduction
A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of the active substance. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No new pharmacokinetic data have been submitted with this application. This is acceptable and in compliance with the bioequivalence guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.), which
specifies that bioequivalence studies are generally not required if the test product is to be administered as an aqueous solution containing the same active substance as the currently approved reference product. Pharmaceutical equivalence has been shown through the comparative physico-chemical characteristics of the proposed product versus the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical efficacy
No new clinical studies were submitted and none were required for this application. A review of intravenous nicardipine was initiated in July 2012 under Article 31 of Directive 2001/83/EC. The CHMP were requested to carry out an assessment of the benefit-risk balance of intravenous nicardipine. Based upon the data made available during the review, the CHMP considered that overall, sufficient evidence is available on the safety and efficacy of nicardipine-containing medical products for intravenous 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.

More information and the assessment report for Article 31 referral: EMEA/H/A-31/1339 can be found on the European Medicines Agency website.

IV.5 Clinical Safety
Under Article 31 of Directive 2001/83/EC, the CHMP reviewed all relevant safety data in the form of suitable literature publications and post marketing safety data in order to determine the safety profile of intravenous nicardipine. 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 intravenous nicardipine. Additionally, significant concerns were raised regarding the administration of intravenous 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 intravenous 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. More information and the assessment report for Article 31 referral: EMEA/H/A-31/1339 can be found on the European Medicines Agency website.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A risk management plan has been developed to ensure that the product is used as safely as possible. Based on this plan, safety information has been included in the approved SmPC and the PIL for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>The risks of hypersensitivity associated with the use of the drug product are described in the SPC Section 4.3, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
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</tr>
<tr>
<td>Injection site reactions</td>
<td>The risks of injection site reactions associated with the use of the drug product are described in the SPC Section 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>Educational materials for healthcare professionals in the form a DHPC and a HCP brochure.</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis and other severe skin reactions</td>
<td>The risks of toxic epidermal necrolysis and other severe skin reactions associated with the use of the drug product are described in the SPC Section 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with severe aortic stenosis</td>
<td>The risks associated with the use of the drug product in patients with severe aortic stenosis are described in the SPC Section 4.3, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with arteriovenous shunt or aortic coarctation</td>
<td>The risk of compensatory hypertension associated with the use of the drug product in patients with arteriovenous shunt or aortic coarctation) are described in the SPC Section 4.3, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with unstable angina or with recent heart attack</td>
<td>The risks associated with the use of the drug product in patients with unstable angina or with recent heart attack are described in the SPC Section 4.3, 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Hypotension</td>
<td>The risks of hypotension associated with the use of the drug product are described in the SPC Section 4.4, 4.5 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Worsening of cardiac insufficiency in patients with cardiac failure, particularly those on beta blockers</td>
<td>The risk of worsening of cardiac insufficiency associated with the use of the drug product in patients with cardiac failure, particularly those on beta blockers are described in the SPC Section 4.4 and 4.5, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>The risks of pulmonary oedema associated with the use of the drug product and the risks associated with use of drug products in patients with pulmonary oedema are described in the SPC Section 4.4, 4.5, 4.6, and 4.8.</td>
<td>None</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>Peripheral oedema</td>
<td>The risks of peripheral oedema associated with the use of the drug product and the risks associated with use of drug products in patients with peripheral oedema are described in the SPC Section 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Safety in pregnancy</td>
<td>The risks associated with the use of the drug product in pregnancy are described in the SPC Section 4.2, 4.4, 4.5, 4.6, and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with history or presence of hepatic impairment</td>
<td>The risks associated with the use of the drug product in patients with history or presence of hepatic impairment, are described in the SPC Section 4.2, 4.4, 4.5, and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with renal impairment</td>
<td>The risks associated with the use of the drug product in patients with renal impairment are described in the SPC Section 4.2, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with portal hypertension</td>
<td>The risks associated with the use of the drug product in patients with portal hypertension are described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>The risks of raised intracranial pressure associated with the use of study drug and the risks associated with the use of the drug product in patients with pre-existing elevated intracranial pressure are described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with cerebral infarction, cerebrovascular accident, cerebrovascular spasm and cerebral syndrome</td>
<td>The risks associated with the use of the drug product in patients with cerebral infarction, cerebrovascular accident, cerebrovascular spasm and cerebral syndrome are described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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</tr>
<tr>
<td>Overdose</td>
<td>The risks associated with the overdose of the drug product are described in the SPC Section 4.9, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Off-label use for prevention of premature labour</td>
<td>The risks associated with the off-label use of the drug product in prevention of premature labour are described in the SPC Section 4.6 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>Educational materials for healthcare professionals in the form a DHPC and a HCP brochure.</td>
</tr>
<tr>
<td>Off-label use, including bolus administration</td>
<td>The risks of using bolus administration (off-label use) of the drug product are described in the SPC Section 4.2 and 4.4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>Educational materials for healthcare professionals in the form a DHPC and a HCP brochure.</td>
</tr>
<tr>
<td>Interaction with magnesium sulphate</td>
<td>The risk associated with simultaneous use of magnesium sulfate is described in the SPC Section 4.4 and 4.5, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with fructose intolerance</td>
<td>The risk associated with the use of the drug product in patients with fructose intolerance is described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
</tbody>
</table>

**Important Potential Risks**

| Use during lactation                              | The SPC section 4.6 and 5.3, states that nicardipine and its metabolites are excreted in human milk at very low concentrations and it is advised that nicardipine should not be used during breastfeeding.                              | None                                                                                                  |
| Reduction of body weight at birth/after birth in the baby | The SPC 4.6 and 5.3 has limited information regarding association of nicardipine use and reduction of body weight at birth/after birth in the baby in humans. Therefore, the drug product should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. | None                                                                                                  |
| Paralytic ileus/intestinal obstruction           | The SPC 4.8, states that paralytic ileus is observed with nicardipine use. If paralytic ileus/intestinal obstruction occur, nicardipine should be discontinued.                                                | None                                                                                                  |
| Extrapyramidal                                   | It has been stated in literature that extrapyramidal symptoms are observed with use                                                                              | None                                                                                                  |
### IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Nicardipine 10 mg/10 ml solution for injection.

### V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

### VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable. Nicardipine 10 mg/10 ml solution for injection has shown to be bioequivalent to the reference product Loxen 10mg/ml solution injectable (Novartis Pharma SAS, France), based on a comparison of the physico-chemical attributes of each product. Therefore, the efficacy and safety profiles of Nicardipine 10 mg/10 ml solution for injection and the reference product Loxen 10mg/ml solution injectable (Novartis Pharma SAS, France) are expected to be the same.

Extensive clinical experience with nicardipine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update section 5.2 of the SmPC to ensure better readability and provide greater clarity on the pharmacokinetic profile of Nicardipine. Additionally to update sections 2, 3, 4.2, 4.3, 4.4, 4.6, 4.7, 5.1, 5.2, 6.5 and 6.6 in line with the QRD template and excipient guideline. Consequentially, the PIL has been updated.</td>
<td>UK/H/4610/001/II/004</td>
<td>SmPC and PIL</td>
<td>07/10/16</td>
<td>18/01/17</td>
<td>Approval</td>
<td>Y (annex 2)</td>
</tr>
</tbody>
</table>
Annex 2

Reference: PL 12762/0450 - 0007
Product: Nicardipine 10 mg/10 ml solution for injection
Marketing Authorisation Holder: Mercury Pharmaceuticals Limited
Active Ingredient(s): Nicardipine hydrochloride

Reason:
This is a Type II variation to update SmPC Section 5.2 to ensure better readability and provide greater clarity on the pharmacokinetic profile of Nicardipine and to update SmPC Sections 2, 3, 4.2, 4.3, 4.4, 4.6, 4.7, 5.1, 5.2, 6.5, and 6.6 and relevant sections of PIL in line with the QRD template and excipient guideline. The changes are to ensure that prescribers and healthcare professionals are aware of product and prescribing information and are able to ensure safe administration.

Supporting Evidence:
Revised SmPc fragments and a revised PIL have been provided.

The proposed SmPC changes are as follows:

**Section 4.7 Effects on ability to drive and use machines**
Added: Nicardipine has no or negligible influence on the ability to drive and use machines

**Section 5.2 Pharmacokinetic properties**
Added: Following intravenous administration, Nicardipine is rapidly absorbed with studies showing the time to onset ranging between 5-15 minutes. Peak plasma levels can reach 184 ng/ml and steady state plasma concentrations of 157 ng/ml achieved within 24-48 hours of continuous infusion.
Added: Studies have shown clinical offset of action to be approximately 15 minutes..

**Sections 2, 3, 4.2, 4.3, 4.4, 4.6, 5.1, 6.5, and 6.6**
Editorial changes

Justification for the above changes is given in an updated Clinical Overview.

Evaluation:
The proposed changes are acceptable.

Conclusion:
The current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The variation is recommended for approval.

Decision:
Approved on 18 January 2017.