Thai Food and Drug Administration (Thai FDA)

Public assessment report

Holdipine®

Nicardipine hydrochloride

Reg no. 1C 15122/61 (NG)

I. INTRODUCTION

Hypertensive crisis is a common condition in intensive care units (ICUs). Such condition accounts for 25 percent of all cases in the ICUs. It can be classified as hypertensive emergency or hypertensive urgency, depends on severity of the patients. Hypertensive emergency is a critical condition that is life-threatening. This condition requires immediate treatment with intravenous antihypertensive drug to reduce blood pressure rapidly. Target organs which are damaged include heart, brain and kidney. Common symptoms are chest pain, shortness of breath and neuronal dysfunction. Each type of hypertensive crises has different required medication, target blood pressure and suitable timeframe to lower blood pressure.

Hypertensive emergency is found in only 1 percent of admitted cases due to hypertension. Nevertheless, it is the mortal condition therefore it is important to identify this condition correctly. Several guidelines including American College of Cardiology Guideline 2017 recommended IV antihypertensive medication for management. One of the suggested drugs is nicardipine with the initial dose 5 mg/h, increasing every 5 min by 2.5 mg/h to maximum 15 mg/h. Contraindication to nicardipine include severe aortic stenosis, compensatory hypertension, unstable angina and use within 8 days after myocardial infarction. Furthermore, severe adverse drug reactions, for examples, bloody urine, bloody cough, increased urinary frequency, irregular heartbeat, and numbness or weakness in an arm or a leg can occur in some patients although some of these side effects are rare.

Holdipine is a generic of nicardipine hydrochloride 1 mg/ml solution for injection. This drug belongs to the pharmacotherapeutic group "selective calcium inhibitors with vascular effects". The mechanism of action at very low concentrations is by inhibiting the influx of calcium into the cell. Its action is produced mainly on arterial smooth muscle. This is reflected in relatively large and rapid changes in blood pressure, with minimal inotropic changes in cardiac function (baroreflex effect). Risk-benefit profile of this drug has been demonstrated for decades since 1988.

Many brand names of nicardipine hydrochloride injection have been approved already in Thailand by the Thai FDA. Some of them have discontinued since. Although its use is sporadic in clinical practice, its availability in Thailand is essential as a life-saving medication.

The applicant has provided the GMP clearance certificate of this manufacturer issued by the Thai FDA.

II. QUALITY ASPECTS

II.1 Introduction

Name:	Holdipine (Nicardipine hydrochloride)
Dosage form and strength:	1 mg/ml solution for injection
Procedure:	Generic drugs
Therapeutic class or indication:	Calcium channel blocker
Packaging:	The primary package is amber type I glass (ampoule). The secondary package is colour printed box.

II.2 Drug substance

Nicardipine hydrochloride

International non-proprietary name (INN):	Nicardipine
United States Adopted Name (USAN):	Nicardipine Hydrochloride
Chemical names:	3,5-Pyridinedicarboxylic acid
Molecular formula:	$C_{26}H_{29}N_3O_6 \cdot HCl$
Relative molecular mass:	515.99
Solubility:	Soluble in methanol; sparingly soluble in ethanol and in chloroform; slightly soluble in water.

An ASMF has been submitted for the drug substance. Detailed information regarding the control of starting materials, reagents and raw materials as well as the control of critical steps and intermediates is provided in the ASMF. No materials of animal or human origin are used in the production of the active substance.

Satisfactory specification tests are in place for all starting materials, residual solvents and heavy metals, and these are supported by relevant certificates of analysis.

Satisfactory information on the validation production batches, on the manufacturing process development and on the methods used in the control of the starting materials were also provided.

All potential impurities have been identified and monitored appropriately. There are specification for specified impurities as the quality control of the drug substance.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Drug product

Pharmaceutical development

The excipients are qualitatively and quantitatively similar to those used in the Reference Drug. Thus drug excipient compatibility would not be an issue and there were no non-compendial excipients used in the proposed formulation.

The container closure system is suitable. The proposed formulation is sensitive to light and there is specific requirement for container closure system to protect the formulation from light.

The sterility test applies to its drug product, and bacterial and mold tests present the negative result.

None of the excipients are of animal/human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the product
The manufacturing process has been adequately described and appropriate in-process controls and intermediate specifications are applied.

The manufacturing process has been validated. It show that the manufacturing process to be suitably controlled and consistently capable of producing drug product that meets the required quality requirements.

Drug product specification
The drug product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been presented for three commercial batches size. All results reported were within proposed specifications and indicate that the process is under control, confirming consistency and uniformity of manufacture.

Stability of the drug product
Supporting evidence has been submitted to demonstrate stability of the product for the shelf life of 2 years. The data are satisfactory; thus, shelf-life of 2 years is recommended.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended for this application.