Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

METOCLOPRAMIDE HYDROCHLORIDE 5 MG/ML SOLUTION FOR INJECTION

(metoclopramide hydrochloride anhydrous)

PL 24598/0087

Noridem Enterprises Limited

LAY SUMMARY

Metoclopramide hydrochloride 5 mg/ml Solution for injection (metoclopramide hydrochloride anhydrous)

This is a summary of the Public Assessment Report (PAR) for Metoclopramide hydrochloride 5 mg/ml Solution for injection. It explains how this product 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 this product.

This product will be referred to as Metoclopramide hydrochloride injection in this lay summary for ease of reading.

For practical information about using Metoclopramide hydrochloride injection, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Metoclopramide hydrochloride injection and what is it for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the United Kingdom (UK) and European Union (EU) called Primperan 10 mg/2 ml solution for injection in ampoule.

Metoclopramide hydrochloride injection is used **in adults**:
- to prevent nausea and vomiting that may occur after surgery
- to treat nausea and vomiting including nausea and vomiting which may occur with a migraine
- to prevent nausea and vomiting caused by radiotherapy.

Metoclopramide hydrochloride injection is used **in children and adolescents (aged 1 – 18 years)** only if other treatment does not work or cannot be used:
- to prevent delayed nausea and vomiting that may occur after chemotherapy
- to treat nausea and vomiting that has occurred after surgery.

How does Metoclopramide hydrochloride injection work?
Metoclopramide hydrochloride injection is an antiemetic. It contains an active substance called “metoclopramide” (metoclopramide hydrochloride anhydrous as metoclopramide hydrochloride monohydrate). It works on a part of the brain that prevents a person from feeling sick (nausea) or being sick (vomiting).

How is Metoclopramide hydrochloride injection used?
The pharmaceutical form of this medicine is a solution for injection and the route of administration is by a slow injection into a vein (over at least three minutes) or by injection into a muscle, administered by a healthcare professional (a doctor or a nurse).

Use in adults
For the treatment of nausea and vomiting including nausea and vomiting which may occur with a migraine and for the prevention of nausea and vomiting caused by radiotherapy: the recommended single dose is 10 mg, repeated up to 3 times daily.

The maximum recommended dose per day is 30 mg or 0.5 mg/kg body weight.

For the prevention of nausea and vomiting that may occur after surgery: a single dose of 10 g is recommended.

Use in children and adolescents aged 1-18 years (all indications)
The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to 3 times daily, given by slow injection into a vein.

The maximum dose in 24 hours is 0.5 mg/kg body weight.

For further information on how Metoclopramide hydrochloride injection is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Metoclopramide hydrochloride injection have been shown in studies?
Metoclopramide hydrochloride injection is a generic medicine that fulfils criteria meaning that no additional studies are required. Metoclopramide hydrochloride injection has been considered a generic medicine of the reference medicine based on a comparison of its physical and chemical characteristics.

What are the possible side effects of Metoclopramide hydrochloride injection?
For the full list of all side effects reported with this medicine Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

As Metoclopramide hydrochloride injection is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

Why was Metoclopramide hydrochloride injection approved?
It was concluded that, Metoclopramide hydrochloride injection has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Metoclopramide hydrochloride injection?
A Risk Management Plan (RMP) has been developed to ensure that Metoclopramide hydrochloride injection is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Metoclopramide hydrochloride injection

A Marketing Authorisation for Metoclopramide hydrochloride injection was granted in the UK on 23 November 2021.

The full PAR for Metoclopramide hydrochloride injection follows this summary.

This summary was last updated in January 2022.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Metoclopramide hydrochloride 5 mg/ml Solution for injection (PL 24598/0087) could be approved.

The product is approved for the following indications:

Adult population

Metoclopramide hydrochloride is indicated in adults for:

- prevention of post-operative nausea and vomiting (PONV)
- symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting
- prevention of radiotherapy induced nausea and vomiting (RINV).

Paediatric population

Metoclopramide hydrochloride is indicated in children (aged 1 – 18 years) for:

- prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option
- treatment of established post-operative nausea and vomiting (PONV) as a second line option.

The active substance, anhydrous metoclopramide hydrochloride (as metoclopramide hydrochloride monohydrate), is a neuroleptic antagonist of dopamine. It prevents vomiting by blocking dopaminergic sites.

This application was approved under Regulation 51B of The Human Medicines Regulations 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product Primperan 10 mg/2 mL solution for injection in ampoule that has been licensed within the United Kingdom (UK) and European Union (EU) for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

A biowaiver was submitted with this application, which was accepted. No bioequivalence study was required and no new clinical studies were provided with this application.

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national Marketing Authorisation was granted in the UK on 23 November 2021.

II QUALITY ASPECTS

II.1 Introduction

This product contains metoclopramide hydrochloride monohydrate equivalent to 5 mg of anhydrous metoclopramide hydrochloride in each ml of solution for injection.

In addition to metoclopramide hydrochloride, this product also contain the excipients sodium

chloride, sodium hydroxide or hydrochloric acid (for pH adjustment) and water for injections.

The finished product is packaged in polypropylene ampoules of 2 mL solution, packed in boxes of 5, 10 (2 x 5 ampoules), 20 (4 x 5 ampoules), 50 (10 x 5 ampoules) or 60 (12 x 5 ampoules).

Each 5 ampoule is overwrapped with a protective polypropylene pouch.

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

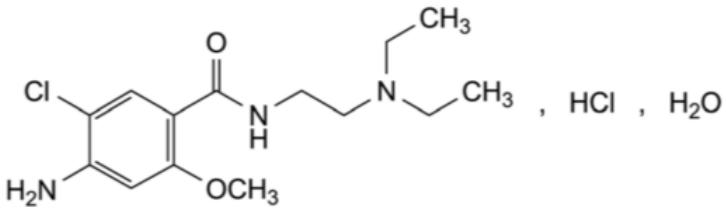
II.2 ACTIVE SUBSTANCE

rINN: Metoclopramide hydrochloride monohydrate

Chemical Name: 4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide hydrochloride monohydrate

Molecular Formula: $C_{14}H_{23}Cl_2N_3O_2. H_2O$

Chemical Structure:



Molecular Weight: 354.3 g/mol

Appearance: White or almost white, crystalline powder or crystals

Solubility: Very soluble in water, freely soluble in ethanol (96 per cent), sparingly soluble in methylene chloride

Metoclopramide hydrochloride monohydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
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II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative physicochemical property profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months, with the storage conditions 'Store the ampoules in the original pouch, in order to protect from light and moisture. This medicinal product does not require any special temperature storage conditions.', acceptable.

The product is for single use only. After first opening of the ampoule: the product must be used immediately.

The product should be used within 2 months after opening the protective pouch.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of metoclopramide hydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of metoclopramide hydrochloride are well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Primperan 10 mg/2 ml solution for injection in ampoule.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

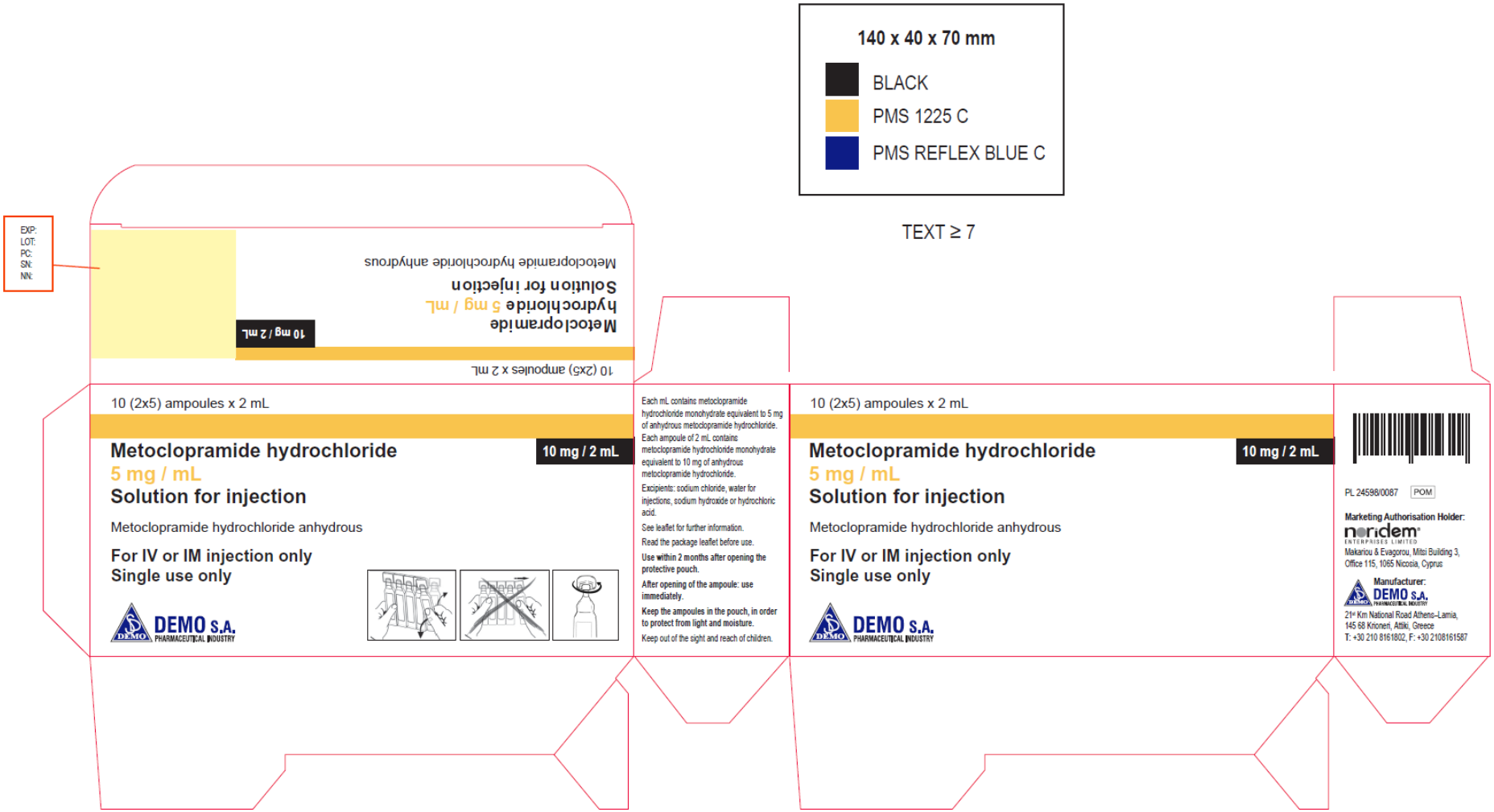
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with metoclopramide hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


140 x 25 x 70 mm
BLACK
PMS 1225 C
EXP:
LOT:
PC:
SN:
NN:
10 mg / 2 mL
Metoclopramide hydrochloride 5 mg / mL
Solution for injection
Metoclopramide hydrochloride anhydrous
For IV or IM injection only. Single use only
5 ampoules x 2 mL
5 ampoules x 2 mL
Metoclopramide hydrochloride 5 mg / mL
Solution for injection
Metoclopramide hydrochloride anhydrous
For IV or IM injection only. Single use only
Each mL contains metoclopramide hydrochloride monohydrate equivalent to 5 mg of anhydrous metoclopramide hydrochloride. Each ampoule of 2 mL contains metoclopramide hydrochloride monohydrate equivalent to 10 mg of anhydrous metoclopramide hydrochloride.
Excipients: sodium chloride, water for injections, sodium hydroxide or hydrochloric acid. See leaflet for further information. Read the package leaflet before use. Use within 2 months after opening the protective pouch. After opening of the ampoule: use immediately. Keep the ampoules in the pouch, in order to protect from light and moisture. Keep out of the sight and reach of children.
DEMO S.A.
PHARMACEUTICAL INDUSTRY
5 ampoules x 2 mL
10 mg / 2 mL
Metoclopramide hydrochloride 5 mg / mL
Solution for injection
Metoclopramide hydrochloride anhydrous
For IV or IM injection only
Single use only
DEMO S.A.
PHARMACEUTICAL INDUSTRY
PL 24598/0087
POM
Marketing Authorisation Holder:
noridem
ENTERPRISES LIMITED
Makariou & Evagorou,
Mitsi Building 3, Office 115,
1065 Nicosia, Cyprus
Manufacturer:
DEMO S.A.
PHARMACEUTICAL INDUSTRY
21st Km National Road Athens-Lamia,
145 68 Kryoneri, Attiki, Greece
T: +30 210 8161602, F: +30 2108161587


140 x 40 x 70 mm
BLACK
PMS 1225 C
PMS REFLEX BLUE C
TEXT ≥ 7
EXP:
LOT:
PC:
SN:
NN:
10 (2x5) ampoules x 2 mL
Metoclopramide hydrochloride anhydrous
Solution for injection
hydrochloride 5 mg / mL
Metoclopramide
10 mg / 2 mL
10 (2x5) ampoules x 2 mL
Metoclopramide hydrochloride
5 mg / mL
Solution for injection
10 mg / 2 mL
Metoclopramide hydrochloride anhydrous
For IV or IM injection only
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Keep out of the sight and reach of children.
10 (2x5) ampoules x 2 mL
Metoclopramide hydrochloride
5 mg / mL
Solution for injection
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For IV or IM injection only
Single use only
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PHARMACEUTICAL INDUSTRY
PL 24598/0087
POM
Marketing Authorisation Holder:
noriclem
ENTERPRISES LIMITED
Makariou & Evagorou, Mitsi Building 3,
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Manufacturer:
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PHARMACEUTICAL INDUSTRY
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140 x 70 x 70 mm
BLACK
PMS 1225 C
PMS REFLEX BLUE C
TEXT ≥ 7
EXP:
LOT:
P.C.:
SN:
NN:
20 (4x5) ampoules x 2 mL
Metoclopramide hydrochloride
5 mg / mL
Solution for injection
Metoclopramide hydrochloride anhydrous
For IV or IM injection only
Single use only
10 mg / 2 mL
DEMO S.A.
Each mL contains metoclopramide hydrochloride monohydrate equivalent to 5 mg of anhydrous metoclopramide hydrochloride. Each ampoule of 2 mL contains metoclopramide hydrochloride monohydrate equivalent to 10 mg of anhydrous metoclopramide hydrochloride.
Excipients: sodium chloride, water for injections, sodium hydroxide or hydrochloric acid.
See leaflet for further information.
Read the package leaflet before use.
Use within 2 months after opening the protective pouch.
After opening of the ampoule: use immediately.
Keep the ampoules in the pouch, in order to protect from light and moisture.
Keep out of the sight and reach of children.
PL 24598/0087
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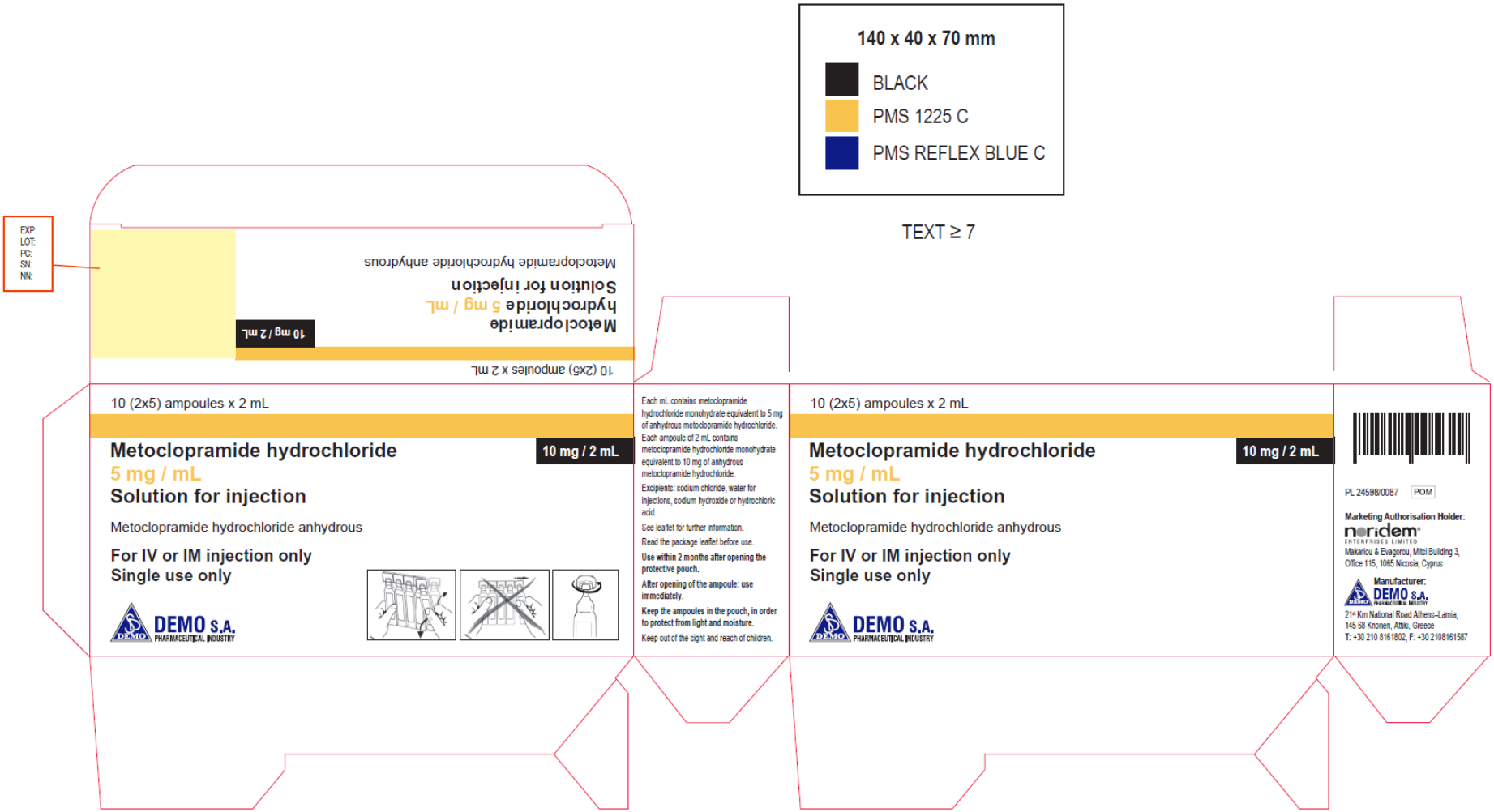
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LOT:
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Solution for injection
hydrochloride 5 mg / mL
Metoclopramide
10 mg / 2 mL
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10 (2x5) ampoules x 2 mL
Metoclopramide hydrochloride
5 mg / mL
Solution for injection
Metoclopramide hydrochloride anhydrous
For IV or IM injection only
Single use only
10 mg / 2 mL
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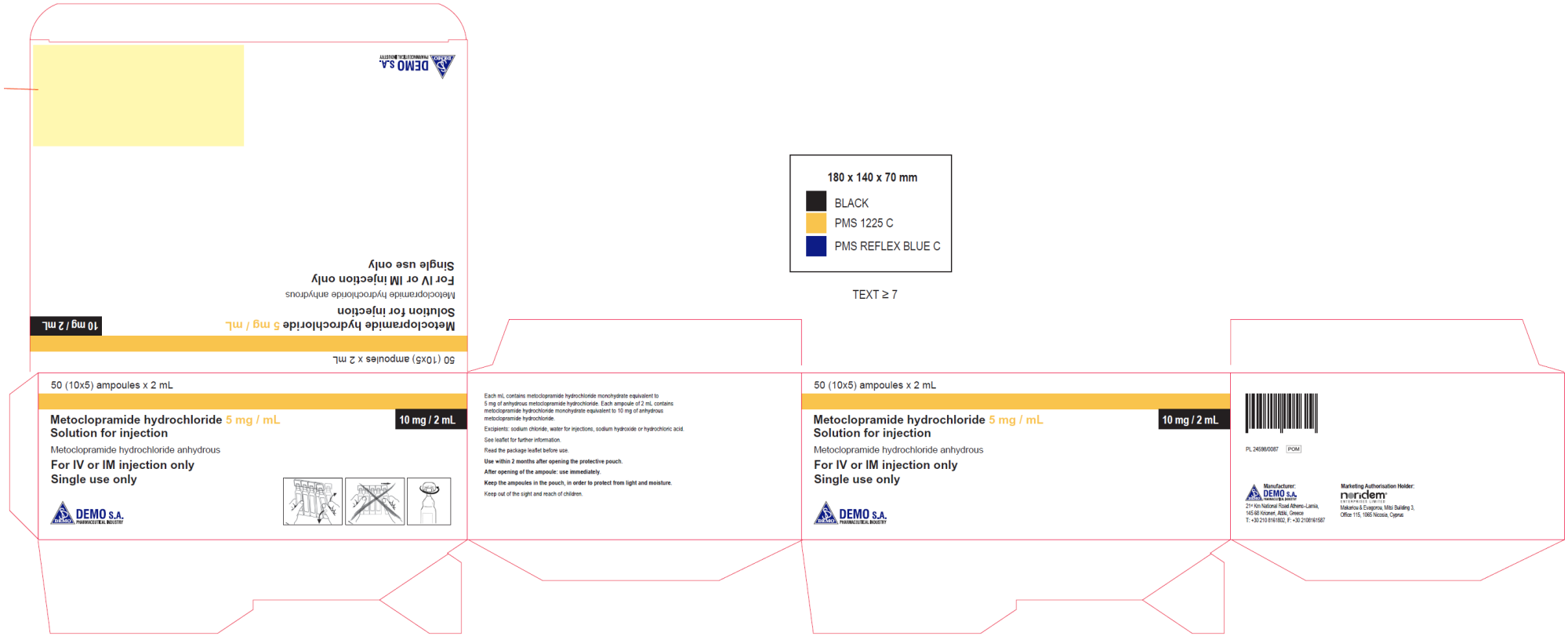
180 x 140 x 70 mm
BLACK
PMS 1225 C
PMS REFLEX BLUE C
TEXT ≥ 7
50 (10x5) ampoules x 2 mL
Metoclopramide hydrochloride 5 mg / mL
Solution for injection
10 mg / 2 mL
Metoclopramide hydrochloride anhydrous
For IV or IM injection only
Single use only
DEMO S.A.
Each mL contains metoclopramide hydrochloride monohydrate equivalent to 5 mg of anhydrous metoclopramide hydrochloride. Each ampoule of 2 mL contains metoclopramide hydrochloride monohydrate equivalent to 10 mg of anhydrous metoclopramide hydrochloride.
Excipients: sodium chloride, water for injections, sodium hydroxide or hydrochloric acid.
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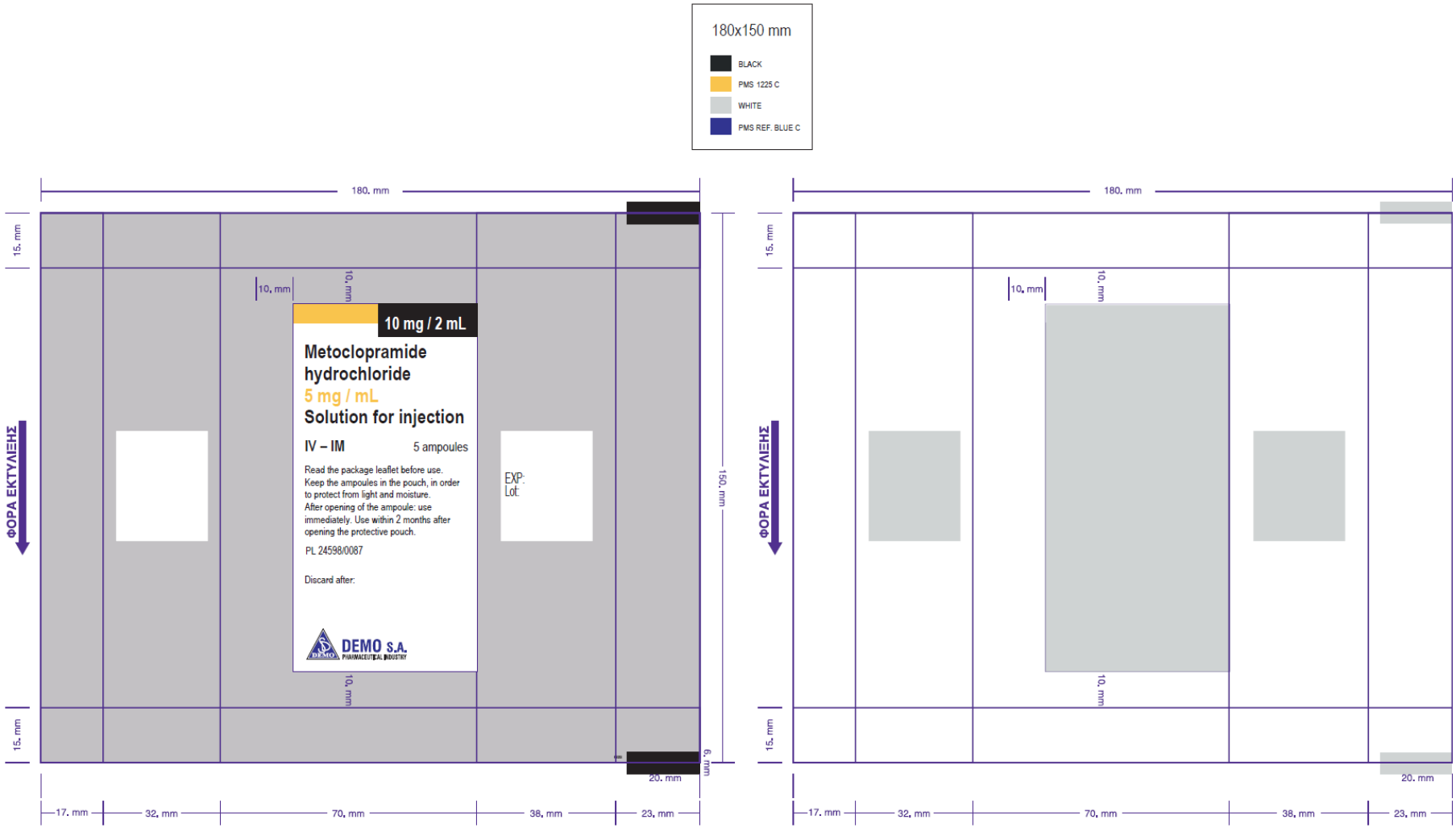
Keep the ampoules in the pouch, in order to protect from light and moisture.
Keep out of the sight and reach of children.
PL 24598/0087
POM
Manufacturer:
DEMO S.A.
Marketing Authorisation Holder:
nordem


220 x 140 x 70 mm
BLACK
PMS 1225 C
PMS REFLEX BLUE C
TEXT ≥ 7
60 (12x5) ampoules x 2 mL
Metoclopramide hydrochloride 5 mg / mL
Solution for injection
Metoclopramide hydrochloride anhydrous
For IV or IM injection only
Single use only
10 mg / 2 mL
DEMO S.A.
60 (12x5) ampoules x 2 mL
Metoclopramide hydrochloride 5 mg / mL
Solution for injection
Metoclopramide hydrochloride anhydrous
For IV or IM injection only
Single use only
10 mg / 2 mL
DEMO S.A.


180x150 mm
BLACK
PMS 1225 C
WHITE
PMS REF. BLUE C
180. mm
15. mm
10. mm
10 mg / 2 mL
Metoclopramide hydrochloride
5 mg / mL
Solution for injection
IV – IM
5 ampoules
Read the package leaflet before use.
Keep the ampoules in the pouch, in order to protect from light and moisture.
After opening of the ampoule: use immediately. Use within 2 months after opening the protective pouch.
PL 24598/0087
Discard after:
EXP:
Lot:
DEMO S.A.
PHARMACEUTICAL INDUSTRY
150. mm
6. mm
20. mm
17. mm
32. mm
70. mm
38. mm
23. mm
ΦΟΡΑ ΕΚΤΥΛΙΞΗΣ

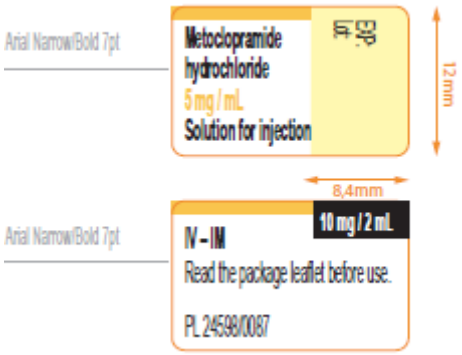

Arial Narrow/Bold 7pt
Metoclopramide
hydrochloride
5 mg / mL
Solution for injection
12mm
8,4mm
Arial Narrow/Bold 7pt
10 mg / 2 mL
IV - IM
Read the package leaflet before use.
PL 24598/0087

TABLE OF CONTENTS OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**