Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Promethazine Hydrochloride 10 mg and 25 mg Film-coated Tablets

(promethazine hydrochloride)

Product Licence Numbers: PL 44041/0170-0171

Noumed Life Sciences Limited

LAY SUMMARY

Promethazine Hydrochloride 10 mg Film-coated Tablets
Promethazine Hydrochloride 25 mg Film-coated Tablets
(Promethazine Hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Promethazine Hydrochloride 10 mg and 25 mg Film-coated Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Promethazine Hydrochloride Film-coated Tablets in this lay summary for ease of reading.

For practical information about using Promethazine Hydrochloride Film-coated Tablets, patients should read the package leaflets or contact their doctor or pharmacist.

What are Promethazine Hydrochloride Film-coated Tablets and what are they used for?

These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Phenergan 10 mg and 25 mg film coated tablets.

Promethazine Hydrochloride Tablets are used to treat the following conditions:
- for short term use, to treat adults with difficulty sleeping (insomnia);
- to treat allergic conditions such as hay fever or rashes (like nettle rash or hives);
- to treat or stop you feeling sick (nausea) or being sick (vomiting) such as travel sickness;
- for short term use: as a sedative for children aged 5 years and above.

How do Promethazine Hydrochloride Film-coated Tablets work?

Promethazine Hydrochloride Tablets contain the active substance promethazine hydrochloride, which belongs to a group of medicines called phenothiazines. It works by blocking a natural substance (histamine) that the body makes during an allergic reaction. It also works directly on the brain to help the patient feel more relaxed.

How are Promethazine Hydrochloride Film-coated Tablets used?

The pharmaceutical form of these medicines is film coated tablets and the route of administration is oral (taken by mouth). The patient should not chew these tablets.

Taking these medicines

The amount the patient needs to take depends on the reason the patient is taking Promethazine Hydrochloride Tablets.
- The patient should not take the tablets for longer than 7 days. If the patient's symptoms worsen or do not improve after 7 days the patient (or the patient's caregiver) should talk to the patient's doctor or pharmacist.
- If the patient feels the effect of their medicine is too weak or too strong, they should not change the dose themselves, but ask their doctor.

The following information will help the patient/caregiver to decide how much the patient needs to take.

Promethazine Hydrochloride 10 mg Film-coated Tablets:
For allergies (such as hay fever, rashes and hives)
Children 2-5 years:
- Other forms of this medicine may be more suitable for children in this age group; the caregiver should ask the child's doctor or pharmacist.

Children 5-10 years:
- A single dose of either one or two tablets (10 mg or 20 mg) given at night or one tablet (10 mg) given twice a day;
- The caregiver should not give the child more than two tablets (20 mg) each day.

Children over 10 years and adults (including the elderly):
- The patient should start with one tablet (10 mg) twice a day;
- This may be increased to a maximum of two tablets (20 mg) three times a day.

For treatment and prevention of feeling sick or being sick (such as travel sickness)
Children 2-5 years:
- Other forms of this medicine may be more suitable for children in this age group; the caregiver should ask the child's doctor or pharmacist.

Children 5-10 years:
- A single tablet to be taken the night before the journey;
- This may be repeated after 6-8 hours if necessary.

Children over 10 years and adults (including the elderly):
- Two tablets (20 mg) to be taken the night before the journey;
- This may be repeated after 6-8 hours if necessary.

As a short term paediatric sedative and for short term treatment of insomnia in adults
Children 2-5 years:
- Other forms of this medicine may be more suitable for children in this age group; the caregiver should ask the child's doctor or pharmacist.

Children 5-10 years:
- Two tablets (20 mg) given as a single dose at night time

Children over 10 years and adults (including the elderly):
- Two to five tablets (2 0mg to 50 mg) as a single dose at night time

Promethazine Hydrochloride 10mg Film-coated Tablets should only be used as recommended. The patient should not exceed the recommended dose.

Promethazine Hydrochloride 25 mg Film-coated Tablets:
For allergies (such as hay fever, rashes and hives)
Children 2-5 years:
- Other forms of this medicine may be more suitable for children in this age group; the caregiver should ask the child's doctor or pharmacist.

Children 5-10 years:
- A single tablet (25 mg) given at night;
- The patient should not be given more than 25 mg each day.

Children over 10 years and adults (including the elderly):
- The patient should start with one tablet (25 mg) taken at night;
- This may be increased to a maximum of one tablet (25 mg) twice a day if necessary.

For treatment and prevention of feeling sick or being sick (such as travel sickness):
Children 2-5 years:
- Other forms of this medicine may be more suitable for children in this age group; the caregiver should ask the child's doctor or pharmacist.

Children 5-10 years
- Promethazine Hydrochloride 10 mg Tablets or other forms of this medicine may be suitable for this age group; the caregiver should ask the child's doctor or pharmacist.

Children over 10 years and adults (including the elderly):
- A single tablet (25 mg) to be taken the night before the journey;
- This may be repeated after 6-8 hours if necessary.

As a short term sedative for children and for short term treatment of insomnia in adults
Children 2-5 years:
- Other forms of this medicine may be more suitable for children in this age group; the caregiver should ask the child's doctor or pharmacist.

Children 5-10 years:
- A single tablet (25 mg) given at night.

Children over 10 years and adults (including the elderly):
- One or two tablets (25 mg-50 mg) taken at night.

If the patient (or the patient's caregiver) feels the effect of Promethazine Hydrochloride 25mg Film-coated Tablets is too weak or too strong, they should not change the dose themselves, but ask the patient's doctor.

Promethazine Hydrochloride 25 mg Film-coated Tablets should only be used as recommended. The patient should not exceed the recommended dose.

For further information on how Promethazine Hydrochloride Film-coated Tablets are used, refer to the package leaflets and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can be obtained without a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient (or the patient' should check with their doctor or pharmacist if they are not sure.

What benefits of Promethazine Hydrochloride Film-coated Tablets have been shown in studies?
Because Promethazine Hydrochloride Film-coated Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that these medicines are

bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Promethazine Hydrochloride Film-coated Tablets?
Because Promethazine Hydrochloride Film-coated Tablets are generic medicines and are bioequivalent to the reference medicines, the benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflets or the SmPCs available on the MHRA website.

Why were Promethazine Hydrochloride Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Promethazine Hydrochloride Film-coated Tablets have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, 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 Promethazine Hydrochloride Film-coated Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Promethazine Hydrochloride Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflets, 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 Promethazine Hydrochloride Film-coated Tablets
Marketing Authorisations for Promethazine Hydrochloride Film-coated Tablets were granted in the UK on 19 November 2020.

The full PAR for Promethazine Hydrochloride Film-coated Tablets follows this summary.

This summary was last updated in January 2021.

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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 applications for Promethazine Hydrochloride 10 mg and 25 mg Film-coated Tablets (PL 44041/0170-0171) could be approved.

The products are approved for the following indications:

- as symptomatic treatment for allergic conditions of the upper respiratory tract and skin including allergic rhinitis, urticaria and anaphylactic reactions to drugs and foreign proteins;
- as an antiemetic;
- for short term use:
  - treatment of insomnia in adults
  - as a paediatric sedative.

The active substance, promethazine hydrochloride, is a potent, long acting, antihistamine with additional anti-emetic, central sedative properties and anti-cholinergic properties.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Phenergan 10 mg and 25 mg film coated tablets, respectively that have been licensed within the UK and the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been in clinical use for over 10 years. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

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

Marketing Authorisations were granted for these products on 19 November 2020.

II QUALITY ASPECTS

II.1 Introduction

These products contain 10 mg and 25 mg of promethazine hydrochloride in each film-coated tablet.

In addition to promethazine hydrochloride, these products also contain the excipients are lactose monohydrate, maize starch, povidone K30, magnesium stearate and the film-coating Opadry Blue (contains titanium dioxide (E171), hypromellose (E464), macrogol/polyethylene glycol (E1521) and indigo carmine aluminium lake blue (E132)).

The finished products are packaged in white polyvinylchloride/polyvinylidene chloride/aluminium with vinyl chloride copolymer blisters, in pack sizes 28, 56, 84 and 100 film-coated tablets. 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.

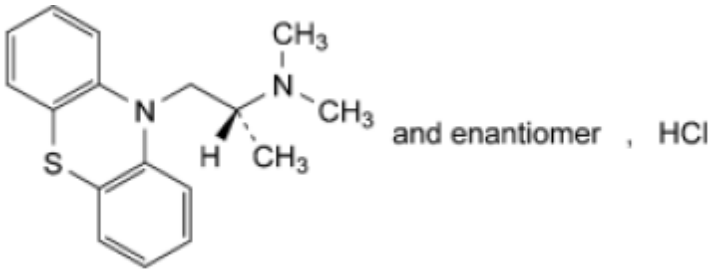
II.2 ACTIVE SUBSTANCES

rINN: Promethazine hydrochloride

Chemical Name: (2RS)-N, N-dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine hydrochloride

Molecular Formula: $C_{17}H_{20}N_2S,HCl$

Chemical Structure:



Molecular Weight: 320.9 g/mol

Appearance: A white or faintly yellowish, crystalline powder

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

Promethazine hydrochloride 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.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution 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.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do contain or consist of genetically modified organisms (GMO).

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

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

Finished Product Specifications
The finished product specifications 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 below 30°C. Store in the original package in order to protect from light.’, is acceptable.

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 Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of promethazine 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 these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of promethazine hydrochloride are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the applications, the applicant submitted the following study.

Bioequivalence study (Fasting conditions)

This study was an open-label, randomised, single-dose, two-treatment, two-sequence, two period, two-way, crossover, oral bioequivalence study comparing the test product Promethazine Hydrochloride 25 mg Tablets versus the reference product Phenergan (promethazine hydrochloride) 25 mg Tablets in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 25 mg tablet; 25 mg) of either treatment with approximately 240 ml of water. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 10 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table 1: Statistical analysis results for the assessment of bioequivalence based on pharmacokinetic parameters of promethazine

PK Parameter	Geometric Least Square Means		Ratio (T/R)%	90% CI ratio	Intra subject CV (5)
	Test (T)	Reference (R)			
Log (C_{max}) (ng/ml)	12.5251	11.2880	110.96	103.60-118.84	15.71
Log (AUC_{0-t}) (ng/ml)	150.6488	136.9582	110.00	101.18-119.57	19.18

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, 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 Marketing Authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. 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

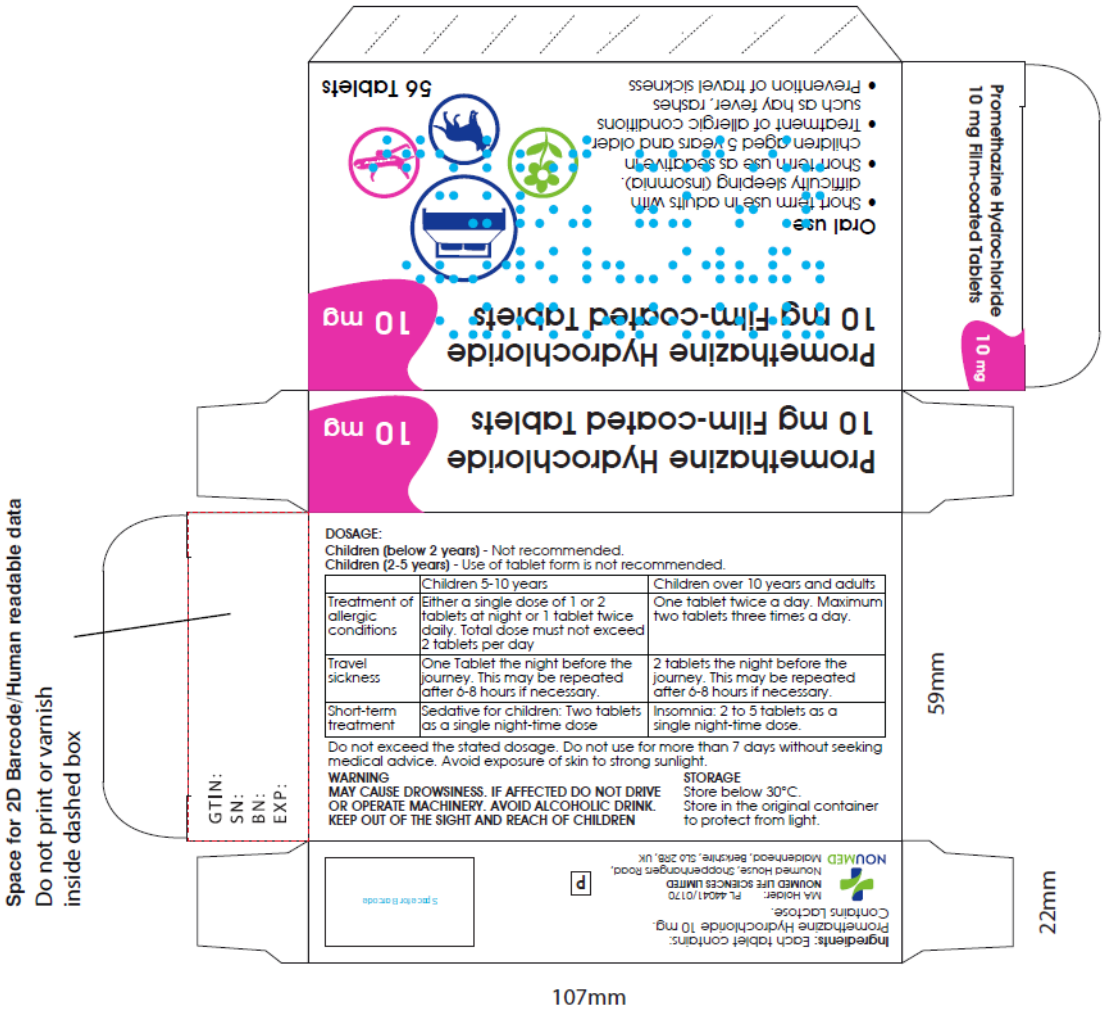
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with promethazine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be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

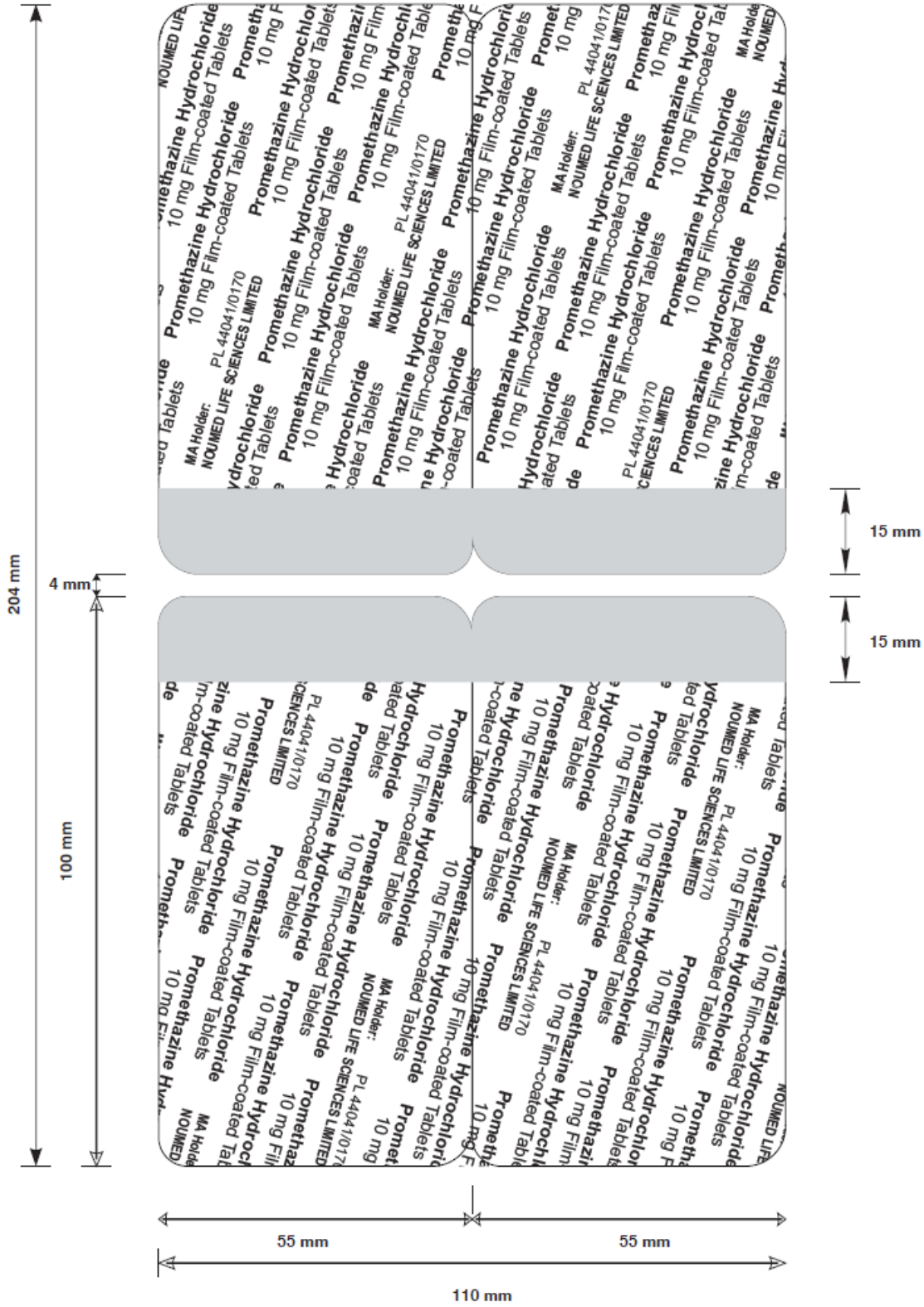
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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

Promethazine Hydrochloride 10 mg Film-coated Tablets

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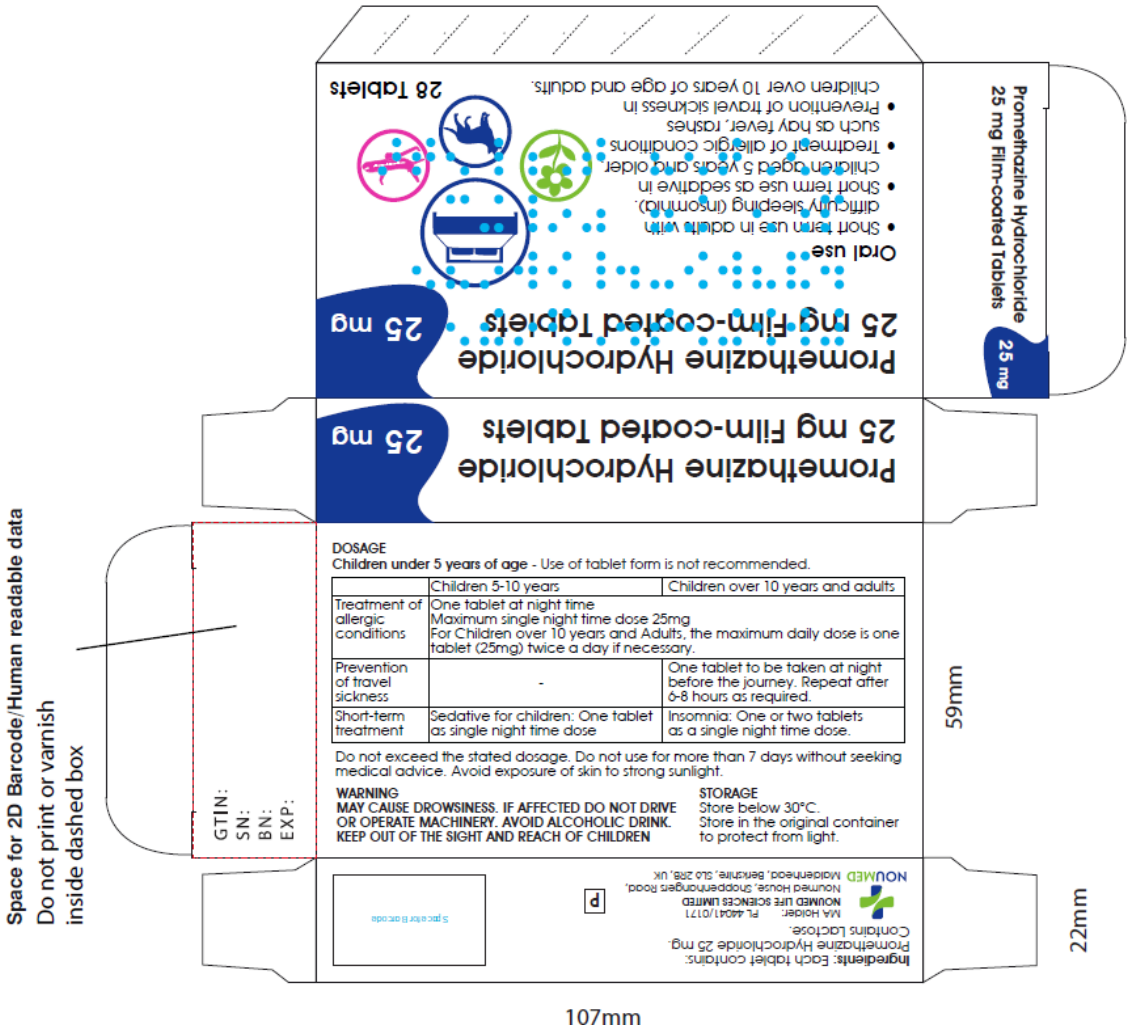
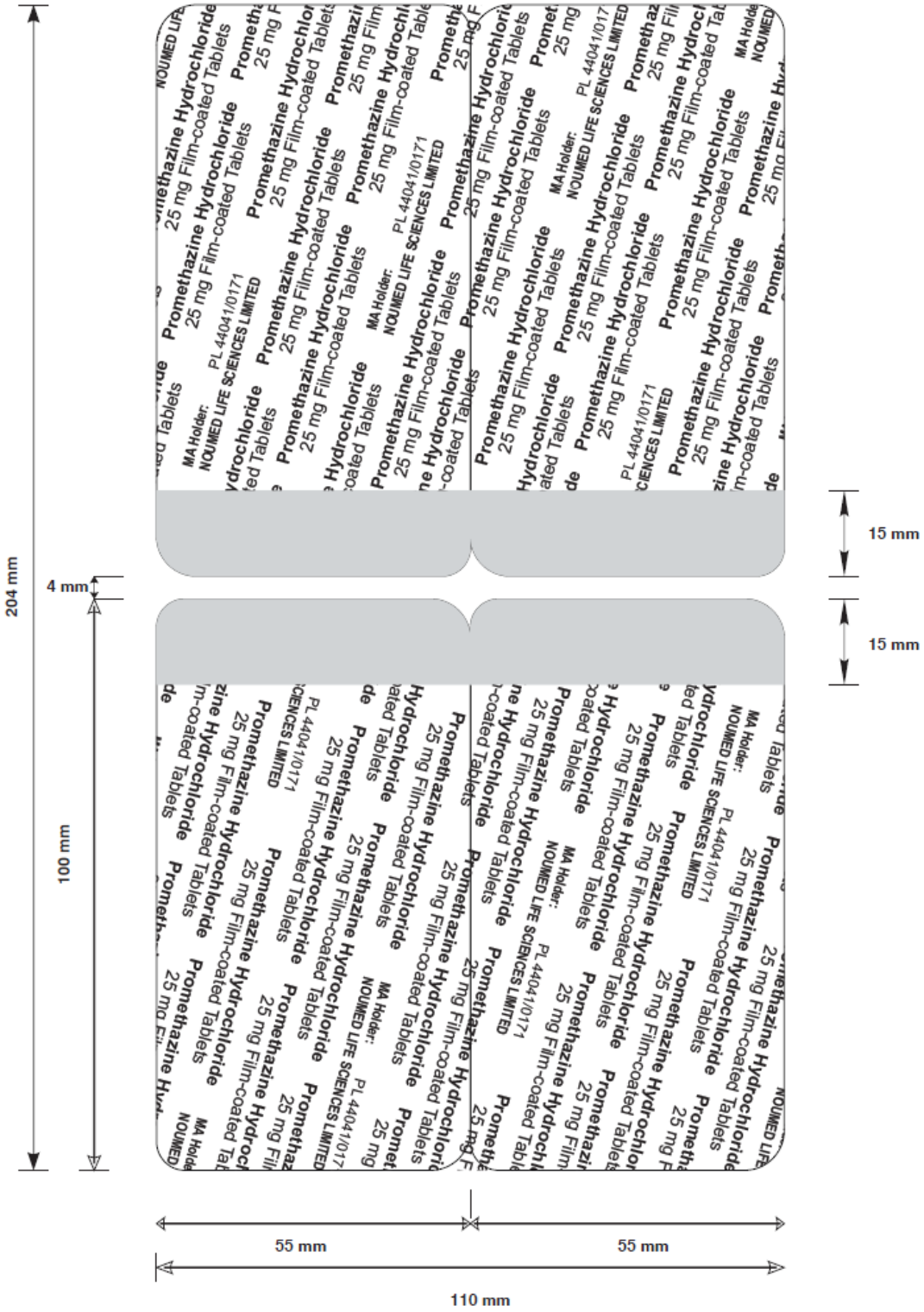
Promethazine Hydrochloride 25 mg Film-coated Tablets

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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**