Public Assessment Report

Decentralised Procedure

Metoclopramide hydrochloride 5mg/5ml Oral Solution

(Metoclopramide hydrochloride)

Procedure No: UK/H/6136/001/DC

UK Licence No: PL 39307/0056

Syri Limited (trading as Thame Laboratories).
LAY SUMMARY

Metoclopramide hydrochloride 5mg/5ml Oral Solution
(metoclopramide hydrochloride, oral solution, 5mg/5ml)

This is a summary of the Public Assessment Report (PAR) for Metoclopramide hydrochloride 5mg/5ml Oral Solution (PL 39307/0056; UK/H/6136/001/DC). It explains how Metoclopramide hydrochloride 5mg/5ml Oral Solution 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 Metoclopramide hydrochloride 5mg/5ml Oral Solution.

The product will be referred to as Metoclopramide throughout the remainder of this PAR.

For practical information about using Metoclopramide, patients should read the package leaflet or contact their doctor or pharmacist.

What is Metoclopramide and what is it used for?
Metoclopramide is a ‘generic medicine’. This means that Metoclopramide is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Primperan 5mg/5ml Oral Solution (Sanofi-Aventis Netherlands B.V).

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

Metoclopramide can be taken with oral painkillers in case of migraine to help painkillers work more effectively.

Metoclopramide is indicated in children (aged 1-18 years) if other treatments do not work or cannot be used to prevent delayed nausea and vomiting that may occur after chemotherapy.

How does Metoclopramide work?
Metoclopramide is an antiemetic. It works on a part of the brain that prevents the patient from feeling sick (nausea) or being sick (vomiting).

How is Metoclopramide used?
The pharmaceutical form of Metoclopramide is an oral solution and the route of administration is via the mouth (oral).

The patient must take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

How much to take
Adult population:
The recommended single dose is 10 mg, repeated up to three times daily.
The maximum recommended dose per day is 30 mg or 0.5 mg/kg body weight.
The maximum recommended treatment duration is 5 days.
To prevent delayed nausea and vomiting that may occur after chemotherapy (children aged 1-18 years):
The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to 3 times daily, taken orally. The maximum dose in 24 hours is 0.5 mg/kg body weight.

Dosing table

<table>
<thead>
<tr>
<th>Age</th>
<th>Body Weight</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 years</td>
<td>10-14 kg</td>
<td>1 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>3-5 years</td>
<td>15-19 kg</td>
<td>2 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>5-9 years</td>
<td>20-29 kg</td>
<td>2.5 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>9-18 years</td>
<td>30-60 kg</td>
<td>5 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>15-18 years</td>
<td>Over 60kg</td>
<td>10 mg</td>
<td>Up to 3 times daily</td>
</tr>
</tbody>
</table>

This medicine should not be taken for more than 5 days to prevent delayed nausea and vomiting that may occur after chemotherapy.

Older people
The dose may need to be reduced depending on kidney problems, liver problems and overall health.

Adults with kidney problems
The patient should talk to their doctor if they have kidney problems. The dose should be reduced if the patient has moderate or severe kidney problems.

Adults with liver problems
The patient should talk to their doctor if they have liver problems. The dose should be reduced if the patient has severe liver problems.

Children and adolescents
Metoclopramide must not be used in children aged less than 1 year.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Metoclopramide can only be obtained with a prescription.

What benefits of Metoclopramide have been shown in studies?
No additional studies were needed as Metoclopramide is a generic medicine that is taken orally, as a solution, and contains the same active substance, in the same concentration, as the reference medicine, Primperan 5mg/5ml Oral Solution (Sanofi-Aventis Netherlands B.V).

What are the possible side effects of Metoclopramide?
Because Metoclopramide is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Metoclopramide, see section 4 of the package leaflet available on the MHRA website.
Why was Metoclopramide approved?
It was concluded that, in accordance with EU requirements, Metoclopramide has been shown to have comparable quality and to be comparable to Primperan 5mg/5ml Oral Solution (Sanofi-Aventis Netherlands B.V). Therefore, the MHRA decided that, as for Primperan 5mg/5ml Oral Solution (Sanofi-Aventis Netherlands B.V), the benefits are greater than their risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Metoclopramide?
A risk management plan (RMP) has been developed to ensure that Metoclopramide 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 Metoclopramide 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/reviewed continuously.

Other information about Metoclopramide
Malta and the UK agreed to grant a Marketing Authorisation for Metoclopramide on 04 August 2016. A Marketing Authorisation was granted in the UK on 19 August 2016.

The full PAR for Metoclopramide follows this summary.

For more information about treatment with Metoclopramide read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2016.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Metoclopramide (PL 39307/0056; UK/H/6136/001/DC) could be approved. The product is a prescription only medicine (POM) and is indicated:

Adult population
Metoclopramide is indicated in adults for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV).
- Prevention of radiotherapy induced nausea and vomiting (RINV).
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting. Metoclopramide can be used in combination with oral analgesics to improve the absorption of analgesics in acute migraine.

Paediatric population
Metoclopramide is indicated in children (aged 1-18 years) for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Malta as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Primperan 5mg/5ml Oral Solution (RVG 05252), which was originally granted in The Netherlands to Sanofi-Aventis Netherlands B.V on 18 December 1968.

Metoclopramide is a substituted benzamide. It is used among other things because of its anti-emetic properties. The anti-emetic effect is the result of two mechanisms of action involving the central nervous system:
- antagonism of the dopaminergic D2 receptors in the chemoreceptor trigger zone and in the vomiting centre of the medulla, which is affected in apomorphine-induced vomiting;
- antagonism of the serotoninergic 5-HT3 receptors and agonist effect on the 5-HT4 receptors which are affected in chemotherapy-induced vomiting.

In addition to the central action, metoclopramide has a stimulant effect on gastrointestinal motility via a peripheral mechanism of action. There is an antidopaminergic effect and potentiation of the effect of acetylcholine. This causes accelerated emptying of the stomach and there is an increase in the pressure exerted by the lower oesophageal sphincter. Metoclopramide has no effect on gastric secretions.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are oral solutions at the time of administration.

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS and CMS considered that the application could be approved at the end of procedure on 04 August 2016. After a subsequent national phase, a licence was granted in the UK on 19 August 2016.
II QUALITY ASPECTS

II.1 Introduction
Each 5ml of oral solution contains 5mg metoclopramide hydrochloride (anhydrous). Other ingredients consist of the following pharmaceutical excipients sodium benzoate (E211), citric acid monohydrate (E330), sodium citrate (E331), saccharin sodium (E954), lemon flavour 13499 (containing propylene glycol (E1520), natural flavouring substances and flavouring preparation) and purified water.

The finished product is packed into Ph. Eur amber (Type III) glass bottles with a tamper evident, child resistant closure (white plastic cap) consisting of a polypropylene inner, polyethylene outer and an expanded polyethylene (EPE) liner. The product is available in a pack size of 150 ml bottles. The bottles are packed in to a cardboard carton together with an oral syringe dosing device and a low-density polyethylene (LDPE) syringe adaptor for bottle. The syringe has a capacity of 5ml and dosing graduations at every 0.2ml. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Metoclopramide hydrochloride
Chemical names: 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide

Structural formula:

\[
\text{\begin{align*}
\text{Cl} & \quad \text{H}_3 \\
\text{H}_2 \text{N} & \quad \text{N} \quad \text{CH}_3 \\
\text{OCH}_3 & \quad \text{Cl} \\
\text{O} & \quad \text{H}_2 \text{O}
\end{align*}}
\]

Molecular formula: \( \text{C}_{14}\text{H}_{23}\text{Cl}_2\text{N}_3\text{O}_2, \text{H}_2\text{O} \)
Molecular mass: 354.3 g/mol
Appearance: White or almost white, crystalline powder or crystals.
Solubility: Very soluble in water, freely soluble in alcohol, sparingly soluble in methylene chloride.

Metoclopramide hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, metoclopramide hydrochloride, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, oral solution containing 5mg metoclopramide hydrochloride (anhydrous) per 5ml of oral solution that is comparable in performance to the originator product Primperan 5mg/5ml Oral Solution (Sanofi-Aventis Netherlands B.V). A satisfactory account of the pharmaceutical development has been provided.
All excipients comply with their respective European Pharmacopoeia monographs with the exception of the lemon flavour which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacture of the product**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

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

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the unopened bottle with no special storage conditions. The in-use shelf life of the product is 60 days after first opening.

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**
There are no objections to the approval of this application from a pharmaceutical viewpoint.
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.

The Marketing Authorisation Holder’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Metoclopramide is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
With reference to the CPMP guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous oral solution containing the same active substance concentration as the approved reference medicinal product. No bioequivalence data have been submitted with this application and none are required.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of metoclopramide hydrochloride.

Based on the data provided, Metoclopramide can be considered bioequivalent to the reference product Primperan 5mg/5ml Oral Solution (Sanofi-Aventis Netherlands B.V).

IV.2 Pharmacokinetics
With reference to the CPMP guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous oral solution containing the same active substance concentration as the approved reference medicinal product. No bioequivalence data have been submitted with this application and none are required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.
IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Metoclopramide.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
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<tbody>
<tr>
<td>• Hypersensitivity to the active substance or any of the excipients</td>
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<tr>
<td>• Use in patients with gastrointestinal haemorrhage, mechanical obstruction or gastrointestinal perforation</td>
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<tr>
<td>• Use in patients with a history of neuroleptic or metoclopramide-induced tardive dyskinesia</td>
</tr>
<tr>
<td>• Increased crises, frequency and intensity of convulsions especially in epileptic patients</td>
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<tr>
<td>• Exacerbation of Parkinson's disease</td>
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<td>• Severe hypertension in patients with confirmed or suspected phaeochromocytoma</td>
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<tr>
<td>• Lack of effect of levodopa or dopaminergic agonists on concomitant use</td>
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<tr>
<td>• Methaemoglobinemia particularly in neonates with NADH cytochrome-b5 deficiency</td>
</tr>
<tr>
<td>• Extrapyramidal disorders in young adults and children less than 1 year of age</td>
</tr>
<tr>
<td>• Tardive dyskinesia after prolonged treatment particularly in elderly patients</td>
</tr>
<tr>
<td>• Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>• Potentiation of sedative effects on concomitant use with central nervous system (CNS) depressants and alcohol</td>
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<tr>
<td>• Use during late pregnancy</td>
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<tr>
<td>• Electrocardiogram: QT prolonged including Torsades de Pointes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Concomitant use with anticholinergics and morphine derivatives leading to effects on gastric motility</td>
</tr>
</tbody>
</table>

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Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

According to the regulatory requirements, the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. No bioequivalence study has been submitted with this application for Metoclopramide and none was required.

The grant of a marketing authorisation is recommended for this application.

V User consultation
The package leaflet 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 language used for the purpose of user testing the PIL was English.

The results show that the package leaflet 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 metoclopramide hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Metoclopramide is presented below: