Public Assessment Report

Decentralised Procedure

Metoclopramide hydrochloride 5mg/5ml oral solution

(metoclopramide hydrochloride)

Procedure No: UK/H/6631/001/DC

UK Licence No: PL 00240/0425

Thornton & Ross Limited trading as STADA
LAY SUMMARY

Metoclopramide hydrochloride 5mg/5ml oral solution

(Metoclopramide hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Metoclopramide hydrochloride 5mg/5ml oral solution PL 00240/0425 formerly PL 27900/0018; UK/H/6631/001/DC. It explains how the application for Metoclopramide hydrochloride 5mg/5ml oral solution was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Metoclopramide hydrochloride 5mg/5ml oral solution. For ease of reading, the product may be referred to as ‘Metoclopramide hydrochloride oral solution’ in this lay summary.

For practical information about using Metoclopramide hydrochloride 5mg/5ml oral solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Metoclopramide hydrochloride oral solution and what is it used for?
Metoclopramide hydrochloride oral solution is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Metoclopramide hydrochloride oral solution is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Metoclopramide hydrochloride oral solution 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.

How does Metoclopramide hydrochloride oral solution work?
Metoclopramide hydrochloride oral solution contains the active substance, metoclopramide hydrochloride, which is an antiemetic. Metoclopramide hydrochloride works on a part of the brain that prevents a patient from feeling sick (nausea) or being sick (vomiting).

How is Metoclopramide hydrochloride oral solution used?
Metoclopramide hydrochloride oral solution is available as an oral solution and is taken by mouth (swallowed).

Metoclopramide hydrochloride oral solution can only be obtained on prescription.

The patient should always take this medicine exactly as his/her doctor or pharmacist has advised. The patient should check with his/her doctor or pharmacist, if he/she is not sure.

A graduated oral syringe is delivered within the packet as a dosing device in order to facilitate accurate dosing. The syringe is suitable for doses up to 5 ml. For dosages over 5 ml the described steps in the package leaflet should be repeated until the required dose is achieved.

Children and adolescents
Metoclopramide hydrochloride oral solution is indicated for use in adults only. Other formulations may be available for the treatment children and adolescents.

Metoclopramide must not be used in children aged less than 1 year (see section 2 of the package leaflet for further information).
Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

**What benefits of Metoclopramide hydrochloride oral solution have been shown in studies?**
As metoclopramide hydrochloride is a well-known substance, and its use in the proposed indications is well-established, the applicant presented data from the scientific literature. The literature confirmed the efficacy and safety of metoclopramide hydrochloride in the proposed indications.

**What are the possible side effects of Metoclopramide hydrochloride oral solution?**
Like all medicines, Metoclopramide hydrochloride oral solution used can cause side effects, although not everybody gets them.

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

For the full list of all side effects reported with Metoclopramide hydrochloride oral solution, see section 4 of the package leaflet.

**Why is Metoclopramide hydrochloride oral solution approved?**
The use of Metoclopramide hydrochloride oral solution in the proposed indications is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Metoclopramide hydrochloride oral solution outweigh the risks and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Metoclopramide hydrochloride oral solution?**
A Risk Management Plan has been developed to ensure that Metoclopramide hydrochloride oral solution 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 hydrochloride oral solution, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Metoclopramide hydrochloride oral solution**
The UK agreed to grant a Marketing Authorisation on 27 September 2018. A Marketing Authorisation was granted in the UK to Renantos Pharmavertriebsgesellschaft mbH on 22 October 2018.

Following a Change of Ownership procedure, the Marketing Authorisation was transferred to Thornton & Ross Limited, trading as STADA (PL 00240/0425) on 23 November 2018.

The full Public Assessment Report approved for Metoclopramide hydrochloride oral solution follows this summary.

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

This summary was last updated in December 2018.
SCIENTIFIC DISCUSSION

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Scientific discussion

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS (UK) considered that the application for Metoclopramide hydrochloride 5mg/5ml oral solution (PL 00240/0425, formerly PL 27900/0018; UK/H/6631/001/DC) could be approved.

The product is a Prescription Only Medicine (POM) and is indicated in adults for the:
- prevention of 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.

The application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS) and Luxembourg as Concerned Member State (CMS); however, Luxembourg was withdrawn as a CMS during the procedure.

The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use. Metoclopramide hydrochloride, the active substance, has been used in clinical practice since the 1960s. It has been extensively used worldwide as a stimulant of upper gastrointestinal motility and in the prevention and treatment of nausea and vomiting associated inter alia with various gastrointestinal disorders, with migraine, after surgery, and with cancer therapy.

Metoclopramide is a derivative of p-aminobenzoic acid and is structurally related to procainamide, but lacks local anaesthetic and antiarrhythmic properties. Metoclopramide differs structurally from procainamide by the presence of 5-chloro and 2-methoxy aryl substituents.

The pharmacology of metoclopramide is complex, involving the gastrointestinal (GI) tract and central nervous system (CNS). Metoclopramide possesses parasympathomimetic activity as well as being a dopamine-receptor (D2) antagonist with a direct effect on the chemoreceptor trigger zone; it also has serotonin-receptor (5-HT3) antagonist properties.

No new non-clinical or clinical studies were conducted to support this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

The UK 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 UK 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 UK considered that the application could be approved at the end of procedure (Day 210) on 27 September 2018. After a subsequent national phase, a Marketing Authorisation for Metoclopramide hydrochloride 5mg/5ml oral solution (PL 27900/0018) was granted in the UK to Renantos Pharmavertiebsgesellschaft mbH on 22 October 2018.

Following a Change of Ownership procedure a Marketing Authorisation (PL 00240/0425) was granted to Thornton & Ross Limited, trading as STADA’ on 23 November 2018.

II. QUALITY ASPECTS
II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a clear, colourless solution.

Each 1 ml or 5 ml oral solution contains 1 mg or 5 mg, respectively, of metoclopramide hydrochloride (as metoclopramide hydrochloride monohydrate).

The product also contains pharmaceutical excipients, namely methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment). Appropriate justification for the inclusion of each excipient has been provided.

The product is supplied in amber 150 ml, glass bottles, (Type III), each with a low-density polyethylene (LDPE) adapter and a screw cap consisting of a white high-density polyethylene (HDPE) cap and a red HDPE originality ring. Each bottle, along with the patient information leaflet, is packed in a carton box with a:
- dosing pipette consisting of a piston and barrel of LDPE and a plunger of polystyrol
- 5 ml oral LDPE syringe with 0.1 ml graduation marks and a polystyrol syringe adaptor for bottle.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE
Metoclopramide hydrochloride monohydrate

INN: Metoclopramide hydrochloride monohydrate
Chemical name: 4-amino-5-chloro-N-[(diethylamino)ethyl]-2-methoxybenzamide hydrochloride monohydrate
Molecular formula: C₁₄H₂₃ClN₃O₂·H₂O
Structure:

![Metoclopramide Structure](image)

Mr: 354.3
Appearance: A 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
Polymorphism: Metoclopramide has not been found to exhibit polymorphism

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 a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCT
Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious, stable oral solution containing 1 mg/1 ml (5mg/5ml) of metoclopramide hydrochloride (as metoclopramide hydrochloride monohydrate). Suitable pharmaceutical development data have been provided for this application.

All the excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.
None of the excipients contain materials of animal or human origin.

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

**Manufacturing Process**
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 with full production-scale batches that have shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full production-scale batches.

**Control of Finished Product**
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specification. 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. Based on the results, a shelf life of 30 months for the unopened product and 6 months after first opening for the opened product (however not exceeding the expiry date stated on the bottle), has been approved.

The approved special storage condition for the product is 'Keep the bottle in the outer carton in order to protect from light. Do not store above 25°C after opening the bottle.'

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

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary for an application of this type.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted, from a quality point of view.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of metoclopramide hydrochloride are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical overview 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**
The pharmacology of the metoclopramide hydrochloride is well known and adequately described in the applicant’s non-clinical overview.

No new data have been submitted and none are required for an application of this type. A brief summary is provided here, further detail is provided in the clinical overview.

The pharmacology of metoclopramide is complex and the mechanism(s) of action of metoclopramide has not yet been fully elucidated. The principal pharmacological effects of the drug involve the gastrointestinal tract and CNS, where it exhibits prokinetic and antiemetic properties.

**III.3 Pharmacokinetics**
No new data have been submitted and none are required for an application of this type. The pharmacokinetics of metoclopramide has been described using both non-clinical and clinical data. The non-clinical expert has provided an in-depth review of the pharmacokinetics characteristics, and the review is largely acceptable. A dedicated section to discuss the potential drug-drug interactions of
Metoclopramide is absent. However, the potential drug-drug interactions of metoclopramide are briefly described in the clinical overview in a manner to support section 4.5 of the Summary of Product Characteristics (SmPC), hence its absence from the non-clinical overview can be accepted.

A brief summary of the pharmacokinetics of metoclopramide is provided here; further detail is provided in the clinical overview.

Metoclopramide is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration.

Bioavailability of metoclopramide appears to correlate with the ratio of free:conjugated metoclopramide concentrations in the urine. It appears that sulphate conjugation in the gastrointestinal lumen and/or during first pass through the liver is the principal determinant of bioavailability of orally administered metoclopramide. The absolute bioavailability of orally administered metoclopramide has not been clearly established in humans. On average, the bioavailability of oral metoclopramide is about 80%, but it varies between about 30 and 100%.

Bioavailability is equally variable after rectal or intranasal doses, although it may be somewhat better if the drug is given intramuscularly. Thus, following intramuscular administration, the absolute bioavailability of metoclopramide is 74-96%.

The distribution of tritiated metoclopramide has been studied in mice by autoradiography. After intra-gastric or intramuscular administration, metoclopramide was located in the intestinal mucosa, the liver and biliary tracts, and the salivary glands. Lesser amounts were found in the central nervous system (CNS), heart, thymus, and suprarenal glands, and in fat and bone marrow. These patterns of distribution were already established at 5 minutes after intramuscular and 1 hour after intra-gastric dosage.

Metoclopramide crosses the blood-brain barrier and enters the CNS in animals, with high concentrations in the area postrema, which contains the chemoreceptor trigger zone (CTZ) for vomiting in man.

Metoclopramide is weakly bound to plasma proteins; in vitro, metoclopramide is 13-30% protein bound, principally to albumin. Metoclopramide also freely crosses the placenta and is excreted in variable amounts in breast milk. Five mothers took 10 mg orally 3 times daily beginning on day 3 to 9 postpartum because of an insufficient milk supply. Metoclopramide in milk samples taken 1 to 2 hours after a 10-mg dose on days 4 and/or 14 ranged from 52 to 157 μg/L. It has been estimated that these infants would receive maximum metoclopramide dosages of 6 to 24 μg/kg daily, and the 5 breastfed infants were also studied. Serum metoclopramide levels were undetectable (< 2 μg/L) in 4 infants; the fifth had serum levels of 20.9 and 18.6 μg/L on days 4 and 14 postpartum, respectively. These levels averaged 8% of the infant’s mother’s metoclopramide serum levels which were very high. Furthermore, a study of neonates who each received a single oral dose of 100 to 150 μg/kg found peak serum levels averaging 17.7 μg/L, which is similar to the levels achieved in the breastfed infant with metoclopramide detectable in serum.

The major metabolite found in the urine is 2-[4-amino-5-chloro-2-methoxybenzoyl]amino]acetic acid; it is not known if this metabolite is pharmacologically active. Metoclopramide is conjugated with sulphuric and/or glucuronic acid.

Plasma concentrations of metoclopramide reportedly decline in a biphasic manner. Although limited data from single-dose studies have suggested that elimination of metoclopramide is dose dependent, other studies using oral doses up to 100 mg have not shown a dose-dependent pharmacokinetic profile. In addition, one pharmacokinetic study using high doses of metoclopramide did not demonstrate dose-dependent elimination.

The plasma half-life (t½) of metoclopramide was reportedly about 60 to 90 minutes in the rat and dog, and approximately 2 hours in the rabbit.
In adult humans, the half-life of metoclopramide in the initial phase (t½α) is approximately 5 minutes, and the half-life in the terminal phase (t½β) ranges from 2.5-6 hours.

In children receiving oral or intravenous metoclopramide, the elimination half-life of the drug reportedly is 4.1-4.5 hours. Following oral administration of 0.15-mg/kg doses of metoclopramide every 6 hours for 10 doses in an infant (3.5 weeks of age), elimination half-lives of 23.1 and 10.3 hours were observed after the first and 10th dose, respectively, which were substantially longer than those reported in older infants, suggesting a reduced clearance in the neonate possibly being associated with immature renal and hepatic functions present at birth.

Metoclopramide and its metabolites are excreted in the urine and the faeces. In a limited number of adults with normal renal function, approximately 85% of an oral dose of radiolabelled metoclopramide was excreted in the urine within 72 hours of administration, principally as unchanged drug and glucuronide or sulphate conjugates of metoclopramide. About 5–10% of an oral dose of metoclopramide is excreted in the urine as 2-[(4-amino-5-chloro-2-methoxybenzoyl)amino]acetic acid and about 20% is excreted unchanged. Approximately 5% of an oral dose of the drug is excreted in the faeces via biliary elimination. Limited evidence indicates that metoclopramide is only minimally removed by haemodialysis or peritoneal dialysis.

### III.4 Toxicology
No new data have been submitted and none are required for an application of this type. The toxicological properties of the metoclopramide hydrochloride are well known and are adequately described in the applicant’s non-clinical overview. A brief summary is provided below.

#### Single dose toxicity
The results of various studies on the acute toxicity of metoclopramide are given inter alia in the database RTECS (Registry of Toxic Effects of Chemical Substances) (RTECS 2014), and the approximate LD₅₀ values of metoclopramide and metoclopramide dihydrochloride monohydrate, determined in diverse animal species for various routes of administration, have been provided.

In animals, lethal doses produced dyspnoea, excessive lacrimation, decreased activity, ataxia, miosis, tachycardia, tremors, and tonic seizures.

A detailed discussion of the potential clinical effects has also been provided, addressing data obtained from clinical experience.

#### Repeat-dose toxicity
There is limited information available from the literature on nonclinical studies on the repeat-dose toxicity of metoclopramide.

In one study, the database reported an approximate intravenous TD₅₀ value of 600 mg/kg after 30 days’ dosing, resulting in weight loss/decreased weight gain and changes in ovarian and uterine weight. In the other study, the database reported an approximate intra-peritoneal TD₅₀ value of 2,399 mg/kg after 8 weeks’ dosing, resulting in haematological and biochemical changes (RTECS 2014).

In a peer review article, (1976) it has been reported that in studies in rabbits and dogs, animals showed signs of fine tremors, hypoactivity, miosis, panting and bizarre positions following intravenous or intramuscular doses of up to 20 mg/kg metoclopramide for 4 to 5 weeks. These signs appeared and disappeared more rapidly with intravenous than with intramuscular administration, but there were no other signs of drug-related effects and no haematological, biochemical or histopathological changes. Furthermore, dogs receiving up to 80 mg/kg metoclopramide for 5 days a week over 16 weeks showed marked behavioural changes only at higher doses, characterised by fine tremors, subdued behaviour, anorexia and miosis (1976).
Genotoxicity
Metoclopramide was evaluated for its genotoxic effects in cultured rodent and human cells. Some evidence of increased clastogenicity was observed in a human lymphocyte study, however only on extended exposure (72 hours). In other provided evidence, however, metoclopramide was positive in the in vitro Chinese hamster lung cell/HGPRT forward mutation assay for mutagenic effects and the in vitro human lymphocyte chromosome aberration assay for clastogenic effects. However, it was negative in the in vitro Ames mutation assay, the in vitro unscheduled DNA synthesis (UDS) assay with rat and human hepatocytes and the in vivo rat micronucleus assay.

Carcinogenicity
In a rat model for assessing the tumour promotion potential, a 2-week oral treatment with metoclopramide at a dose of 260 mg/kg/d (about 35 times the maximum recommended human dose based on body surface area) enhanced the tumorigenic effect of N-nitrosodiethylamine (2011).

No abnormal haematological, biochemical or histopathological changes in rats receiving daily oral doses of up to 40 mg/kg or 100 mg/kg for 77 weeks or 3-6 months, respectively.

A similar regimen of 300 mg/kg slowed growth and weight gain in some animals, while 600 mg/kg resulted in the death of the majority of animals within the dosage period. Dogs receiving up to 40 mg/kg daily for 5 days a week showed behavioural changes like those observed in the sub-chronic studies, to which tolerance did not develop over 54 weeks.

An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. The drug manual AHFS (2014) points out that although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents (e.g., phenothiazines), no clinical or epidemiological studies conducted to date have shown an association between long-term administration of prolactin-stimulating drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive at this time. Since in vitro tests indicate that approximately one-third of human breast cancers are prolactin-dependent, metoclopramide should be used with caution in patients with previously detected breast cancer.

Reproductive and developmental toxicity
Metoclopramide freely crosses the placenta. Nonetheless, there were no abnormalities, or drug-related effects on fetal size and weight, in the offspring of mice, rats and rabbits treated with up to 10 mg/kg metoclopramide daily by the oral, subcutaneous or intravenous routes and at various stages of gestation.

Detailed discussion of the reproductive effects of metoclopramide is provided, this is adequately reflected in the proposed SmPC.

With respect to the clinical experience with metoclopramide in pregnancy, it has to be considered that metoclopramide has often been used to treat nausea and vomiting in pregnancy. A prospective, multicentre, international study (2002) on 175 pregnant women who received metoclopramide and consulted six teratogen information centres in Israel, Italy, Brazil and Canada indicate that metoclopramide use during the first trimester of pregnancy does not appear to be associated with an increased risk of malformations, spontaneous abortions, or decreased birth weight. A large retrospective cohort study (2009) on a total of 3,458 women who were exposed to metoclopramide during the first trimester of pregnancy confirmed that exposure to metoclopramide in the first trimester is not associated with adverse effects on the fetus, including congenital malformations, perinatal death and low birth-weight.

A large amount of data on pregnant women (more than 1,000 exposed outcomes) indicates no malformative toxicity nor fetotoxicity. Accordingly, metoclopramide can be used during pregnancy if clinically needed.

However, due to the pharmacological properties (as other neuroleptics), in the case of metoclopramide administration at the end of pregnancy, extrapyramidal syndrome in the newborn cannot be excluded.
Metoclopramide hydrochloride 5mg/5ml oral solution

Metoclopramide should therefore be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.

It is not known whether metoclopramide affects fertility in humans, although it is shown to be excreted in variable amount in breast milk, and so metoclopramide is not recommended during breastfeeding.

Local tolerance
There are no data available from the literature on specific nonclinical studies on the local tolerance of orally applied metoclopramide. However, a body of clinical tolerance evidence is available based upon nasal and rectal routes of administration which does not raise any specific concern.

Other toxicity studies
Regarding the drug substance and the final drug product, the residual solvents and excipients in the formulation are discussed and raise no toxicological concerns.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for substitution of already authorised products, it is not expected that environmental exposure of metoclopramide hydrochloride will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology, safety and efficacy of metoclopramide hydrochloride is well-known.

The legal basis of this application is a well-established medicinal use application according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic references.

The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

IV.2 Pharmacokinetics
The pharmacokinetic properties of metoclopramide hydrochloride are well known and are adequately described in the applicant's clinical overview. No new pharmacokinetic data were submitted, and none are required for this type of application.

IV.3 Pharmacodynamics
The clinical pharmacodynamic properties of metoclopramide hydrochloride are well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

IV.4 Clinical Efficacy
The clinical efficacy of metoclopramide hydrochloride is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
The safety profile of metoclopramide hydrochloride is well known. No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan, 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 hydrochloride oral solution.
A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular events (bradycardia, syncope, cardiac arrest, QT-prolongation including Torsade de pointes)</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal disorders in children</td>
<td></td>
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<tr>
<td>Tardive dyskinesias, especially in elderly patients on long-term therapy</td>
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<tr>
<td>Anaphylactic reactions</td>
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<tr>
<td>Interaction with serotonergic drugs leading to serotonin syndrome</td>
<td></td>
</tr>
<tr>
<td>Methaemoglobinemia</td>
<td></td>
</tr>
<tr>
<td>Malignant neuroleptic syndrome</td>
<td></td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td></td>
</tr>
</tbody>
</table>

| Important potential risks                                      | None |
| Missing information                                            | None |

In line with other products containing this active, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the Patient Information Leaflet). This is acceptable.

**IV.7 Discussion of the clinical aspects**

It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

**V. USER CONSULTATION**

A 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 pack leaflet 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 product is acceptable, and no new non-clinical safety concerns have been identified. The application contains an adequate review of published clinical data. The Applicant has bridged the literature to the specific formulation of Metoclopramide hydrochloride 5 mg/5 ml oral solution. The published literature supports the efficacy of the product in the proposed indication and posology.

The overall benefit/risk balance is considered to be positive.

The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website.

The labelling text is that agreed at the end of the Decentralised Procedure (UK/H/6631/001/DC). The Marketing Authorisation Holder has committed to submitting the mock-up labelling to the regulatory authorities for approval before packs are marketed. The current labelling text is presented below:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Carton for bottle

1. **NAME OF THE MEDICINAL PRODUCT**

Metoclopramide hydrochloride 5 mg/5 ml oral solution

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1 ml oral solution contains 1 mg metoclopramide hydrochloride (as metoclopramide hydrochloride monohydrate)
5 ml oral solution contains 5 mg metoclopramide hydrochloride (as metoclopramide hydrochloride monohydrate)

3. **LIST OF EXCIPIENTS**

Contains methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and sodium.
See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Oral solution
Clear, colourless liquid.
150 ml oral solution

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP:
Shelf life after first opening: 6 months but not exceeding the expiry date stated on the bottle.
Opened:

9. **SPECIAL STORAGE CONDITIONS**

Keep the bottle in the outer carton in order to protect from light.
Do not store above 25 °C after opening the bottle.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

STADA, Linthwaite, Huddersfield, HD7 5QH, UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 00240/0425

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Metoclopramide hydrochloride 5 mg/5 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

bottle label

1. NAME OF THE MEDICINAL PRODUCT

Metoclopramide hydrochloride 5 mg/5 ml oral solution

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml oral solution contains 1 mg metoclopramide hydrochloride (as metoclopramide hydrochloride monohydrate)
5 ml oral solution contains 5 mg metoclopramide hydrochloride (as metoclopramide hydrochloride monohydrate)

3. LIST OF EXCIPIENTS

Contains methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
Clear, colourless liquid
Bottles of 150 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life after first opening: 6 months but not exceeding the expiry date stated on the bottle.

Opened:

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.
Do not store above 25 °C after opening the bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

STADA, Linthwaite, Huddersfield, HD7 5QH, UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00240/0425

13. **BATCH NUMBER**

Lot {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Metoclopramide hydrochloride 5 mg/5 ml
**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 Y/N (version)</th>
</tr>
</thead>
</table>