12th December 2014

Dear Healthcare Professional,

Metoclopramide: updated indications and posology to minimise risk of (mainly neurological) adverse effects

UK marketing authorisation holders, the European Medicines Agency and the MHRA would like to inform you of the following updated advice following a European review of the benefits and risks of metoclopramide.

Summary of new advice

Limited dose and duration of use

- Metoclopramide should only be prescribed for short-term use (up to a maximum of 5 days) at recommended doses and dose-intervals. This is in order to minimise the risks of neurological and other adverse reactions.
- Intravenous doses should be administered as a slow bolus (at least over 3 minutes) to minimise the risk of occurrence of adverse reactions, including cardiovascular reactions.

Indications for use are restricted as follows:

Adult patients

- Metoclopramide is indicated for short-term use in the prevention and treatment of nausea and vomiting, including that associated with chemotherapy, radiotherapy, surgery and migraine. For detailed indications, please refer to the full list of indications in the recommendations listed in Summary of Product Characteristics (SmPC) and package leaflet (Annex 1 and 2).
- The maximum dose in 24 hours is 30mg, which can be divided into10 mg three times a day (or 0.5mg/kg body weight), by the oral, rectal, intravenous or intramuscular route.
- The maximum recommended treatment duration is 5 days.

Paediatric patients (aged 1-18 years)

- Metoclopramide should be restricted to use as a second line option in children in the following indications:
  - treatment of established post-operative nausea and vomiting (intravenous route only)
  - prevention of delayed chemotherapy-induced nausea and vomiting (oral or intravenous routes only).
- The recommended dose is 0.1 to 0.15mg/kg body weight, repeated up to three times daily. The maximum dose in 24 hours is 0.5mg/kg body weight.
- Oral solutions should be administered using a graduated oral syringe to ensure accuracy.

Paediatric patients (aged 0-1 year)

- Metoclopramide is contraindicated in children less than 1 year of age, and should not be used in any circumstances because of the risk of neurological reactions and methaemoglobinaemia.

For more information please see the Summary of Product Characteristics (SmPC) and package leaflet attached (Annex 1 and 2).

Further information

In December 2011, a European review of the balance of benefits versus risks of metoclopramide, including a consideration of different age groups was initiated by the European Medicines Agency. This was triggered by the French national authority, because of efficacy and safety concerns related to neurological and cardiovascular toxicity.

The review has confirmed a well-established safety profile for metoclopramide, including the risks of neurological adverse effects (e.g. acute extrapyramidal symptoms and irreversible tardive dyskinesia). The risk of these adverse effects is increased in high dose or long term treatment. The risk is also higher in children than in adults.

In chronic conditions the risks of neurological adverse reactions outweigh the benefits. Therefore metoclopramide should not be used in these chronic indications (eg, gastroparesis, dyspepsia, gastro-oesophageal reflux disease).

In children, metoclopramide should be restricted to second line treatment of established post-operative nausea and vomiting and prevention of delayed chemotherapy induced nausea and vomiting. In all other indications, the risks of neurological adverse reactions outweigh the benefits.

Particular care should be taken in relation to doses and dose-intervals when prescribing and administering metoclopramide to children. A paediatric dosing table has been added in the SmPC. Full prescribing information can be found in the Summary of Product Characteristics (Annex 1).

Given very rare reports of serious cardiovascular reactions associated with metoclopramide, particularly via the intravenous route, special care should be given to at-risk populations including: the elderly population, patients with cardiac conduction disturbances (including QT prolongation), uncorrected electrolyte imbalance, bradycardia, and those taking other drugs known to prolong QT interval.

Please share this information with relevant colleagues and health care personnel.

The Product Information of all metoclopramide containing products will be updated to reflect these data.

Call for reporting

Any suspected adverse events should be reported to the National Spontaneous Reporting System according to the National Regulation.

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. Please report:

- all suspected ADRs particularly those that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.

- all suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼

It is easiest and quickest to report ADRs online via the Yellow Cards website: www.mhra.gov.uk/yellowcard

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD" (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- Or by downloading and printing a form from the Yellow Card section of the MHRA website

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates and product name.

Suspected adverse events should also be reported to the relevant Marketing Authorisation holder.

This information is being provided jointly by the Marketing Authorisation holders listed in Annex 3. Contact details are provided if you wish to request further information.

Yours sincerely

Marketing Authorisation Holders listed in Annex 3.

Annexes

1. Summary of Product Characteristics (Commission decision)
2. Package Leaflet (Commission decision)
3. List of other participating marketing authorisation holders and their details

Key Elements from the Summary of Product Characteristics (SmPC)

The information below is relevant for all routes of administration of metoclopramide unless otherwise specified. Please refer to the SmPCs for individual products for full prescribing information.

4.1 Therapeutic indications

Parenteral route/IM-IV

Adult population

Metoclopramide 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 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

Oral route

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

4.2 Posology and method of administration

Parenteral route

The solution can be administered intravenously or intramuscularly.
Intravenous doses should be administered as a slow bolus (at least over 3 minutes).

All indications (adult patients)

For prevention of PONV a single dose of 10mg is recommended.
For the symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting and for the prevention of radiotherapy induced nausea and vomiting (RINV): the recommended single dose is 10 mg, repeated up to three times daily

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

The injectable treatment duration should be as short as possible and transfer to oral treatment should be made as soon as possible.

All indications (paediatric patients aged 1-18 years)

The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to three times daily by intravenous route. The maximum dose in 24 hours is 0.5 mg/kg body weight.

Dosing table

Age	**Body Weight**	**Dose**	**Frequency**
1-3 years	10-14 kg	1 mg	Up to 3 times daily
3-5 years	15-19 kg	2 mg	Up to 3 times daily
5-9 years	20-29 kg	2.5 mg	Up to 3 times daily
9-18 years	30-60 kg	5 mg	Up to 3 times daily
15-18 years	Over 60kg	10 mg	Up to 3 times daily

The maximum treatment duration is 48 hours for treatment of established post-operative nausea and vomiting (PONV).

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

Oral route
All indications (adult patients)

For immediate release preparations
The recommended single dose is 10 mg, repeated up to three times daily.

For prolonged release preparations
15mg strength
The recommended single dose is 15 mg, repeated up to twice daily.
30mg strength
The recommended dose is 30mg once daily.

For all preparations
The maximum recommended daily dose is 30 mg or 0.5mg/kg body weight.
The maximum recommended treatment duration is 5 days.

Prevention of delayed chemotherapy induced nausea and vomiting (CINV) (paediatric patients aged 1-18 years)
The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to three times daily by oral route. The maximum dose in 24 hours is 0.5 mg/kg body weight.

Dosing table

Age	**Body Weight**	**Dose**	**Frequency**
1-3 years	10-14 kg	1 mg	Up to 3 times daily
3-5 years	15-19 kg	2 mg	Up to 3 times daily
5-9 years	20-29 kg	2.5 mg	Up to 3 times daily
9-18 years	30-60 kg	5 mg	Up to 3 times daily
15-18 years	Over 60kg	10 mg	Up to 3 times daily

[*Appropriate measuring device must be provided with the product, and instructions for use must be included in the SmPC*]
The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

For tablets/capsules/granules

Please refer to the SmPC for individual products for additional information regarding posologies

adaptation-implemented in the SmPC depending on the strength of the formulations

For formulations which cannot be used to administer a 5mg dose
Tablets/capsules/granules are not suitable for use in children weighing less than 61 kg.
Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

For formulations which can be used to administer a 5mg dose

Tablets/capsules/granules are not suitable for use in children weighing less than 30 kg.

Other pharmaceutical forms/strengths may be more appropriate for administration to this population

All routes of administration at the exception prolonged release preparations

Method of administration:

A minimal interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose (see section 4.4).

15mg strength prolonged release preparations

Method of administration:

A minimal interval of 12 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose (see section 4.4).

30 mg strength prolonged release preparations

Method of administration:

A minimal interval of 24 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose (see section 4.4).

All routes of administration

Special population

Elderly

In elderly patients a dose reduction should be considered, based on renal and hepatic function and overall frailty.

Renal impairment:

In patients with end stage renal disease (Creatinine clearance ≤ 15 ml/min), the daily dose should be reduced by 75%.

In patients with moderate to severe renal impairment (Creatinine clearance 15-60 ml/min), the dose should be reduced by 50% (see section 5.2).

Hepatic impairment:

In patients with severe hepatic impairment, the dose should be reduced by 50% (see section 5.2).

Paediatric population

Metoclopramide is contraindicated in children aged less than 1 year (see section 4.3).

4.3 Contraindications

For all formulations

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk

- Confirmed or suspected pheochromocytoma, due to the risk of severe hypertension episodes

- History of neuroleptic or metoclopramide-induced tardive dyskinesia

- Epilepsy (increased crises frequency and intensity)

- Parkinson's disease

- Combination with levodopa or dopaminergic agonists (see section 4.5)

- Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency.

- Use in children less than 1 year of age due to an increased risk of extrapyramidal disorders (see section 4.4)

4.4 Special warnings and precautions for use

For all routes of administration at the exception of prolonged release preparations

Neurological Disorders

Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions occur usually at the beginning of the treatment and can occur after a single administration. Metoclopramide should be discontinued immediately in the event of extrapyramidal symptoms. These effects are generally completely reversible after treatment discontinuation, but may require a symptomatic treatment (benzodiazepines in children and/or anticholinergic anti-Parkinsonian medicinal products in adults).

The time interval of at least 6 hours specified in the section 4.2 should be respected between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.

Prolonged treatment with metoclopramide may cause tardive dyskinesia, potentially irreversible, especially in the elderly. Treatment should not exceed 3 months because of the risk of tardive dyskinesia (see section 4.8). Treatment must be discontinued if clinical signs of tardive dyskinesia appear.

Neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy (see section 4.8). Metoclopramide should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting drugs (see section 4.3)

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

For the 15 mg strength prolonged release preparations

Neurological Disorders

Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions occur usually at the beginning of the treatment and can occur after a single administration. Metoclopramide should be discontinued immediately in the event of extrapyramidal symptoms. These effects are generally completely reversible after treatment discontinuation, but may require a symptomatic treatment (benzodiazepines in children and/or anticholinergic anti-Parkinsonian medicinal products in adults).

The time interval of at least 12 hours specified in the section 4.2 should be respected between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.

Prolonged treatment with metoclopramide may cause tardive dyskinesia, potentially irreversible, especially in the elderly. Treatment should not exceed 3 months because of the risk of tardive dyskinesia (see section 4.8). Treatment must be discontinued if clinical signs of tardive dyskinesia appear.

Neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy (see section 4.8). Metoclopramide should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting drugs (see section 4.3)

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

For the 30 mg strength prolonged release preparations

Neurological Disorders

Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions occur usually at the beginning of the treatment and can occur after a single administration. Metoclopramide should be discontinued immediately in the event of extrapyramidal symptoms. These effects are generally completely reversible after treatment discontinuation, but may require a symptomatic treatment (benzodiazepines in children and/or anticholinergic anti-Parkinsonian medicinal products in adults).

The time interval of at least 24 hours specified in the section 4.2 should be respected between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.

Prolonged treatment with metoclopramide may cause tardive dyskinesia, potentially irreversible, especially in the elderly. Treatment should not exceed 3 months because of the risk of tardive dyskinesia (see section 4.8). Treatment must be discontinued if clinical signs of tardive dyskinesia appear.

Neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy (see section 4.8). Metoclopramide should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting drugs (see section 4.3)

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

For all routes of administration

Methaemoglobinemia

Methemoglobinemia which could be related to NADH cytochrome b5 reductase deficiency has been reported. In such cases, metoclopramide should be immediately and permanently discontinued and appropriate measures initiated (such as treatment with methylene blue).

Cardiac Disorders

There have been reports of serious cardiovascular undesirable effects including cases of circulatory collapse, severe bradycardia, cardiac arrest and QT prolongation following administration of metoclopramide by injection, particularly via the intravenous route (see section 4.8).

Special care should be taken when administering metoclopramide, particularly via the intravenous route to the elderly population, to patients with cardiac conduction disturbances (including QT prolongation), patients with uncorrected electrolyte imbalance, bradycardia and those taking other drugs known to prolong QT interval.

Intravenous doses should be administered as a slow bolus (at least over 3 minutes) in order to reduce the risk of adverse effects (e.g. hypotension, akathisia).

Renal and Hepatic Impairment

In patients with renal impairment or with severe hepatic impairment, a dose reduction is recommended (see section 4.2).

Please refer to the SmPC for individual products for additional warnings about excipients.

4.5 Interaction with other medicinal products and other forms of interaction

All routes of administration

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section 4.3).

Combination to be avoided

Alcohol potentiates the sedative effect of metoclopramide.

Combination to be taken into account

Due to the prokinetic effect of metoclopramide, the absorption of certain drugs may be modified.

Anticholinergics and morphine derivatives

Anticholinergics and morphine derivatives may have both a mutual antagonism with metoclopramide on the digestive tract motility.

Central nervous system depressants (morphine derivatives, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related)

Sedative effects of Central Nervous System depressants and metoclopramide are potentiated.

Neuroleptics

Metoclopramide may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.

Serotonergic drugs

The use of metoclopramide with serotonergic drugs such as SSRIs may increase the risk of serotonin syndrome.

Digoxin

Metoclopramide may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Cyclosporine

Metoclopramide increases cyclosporine bioavailability (Cmax by 46% and exposure by 22%). Careful monitoring of cyclosporine plasma concentration is required. The clinical consequence is uncertain.

Mivacurium and suxamethonium

Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

Strong CYP2D6 inhibitors

Metoclopramide exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine and paroxetine. Although the clinical significance is uncertain, patients should be monitored for adverse reactions.

4.6 Fertility, pregnancy and lactation

All routes of administration

Pregnancy A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative toxicity nor foetotoxicity. Metoclopramide can be used during pregnancy if clinically needed. Due to pharmacological properties (as other neuroleptics), in case of metoclopramide administration at the end of pregnancy, extrapyramidal syndrome in newborn cannot be excluded. Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.

Breastfeeding
Metoclopramide is excreted in breast milk at low level. Adverse reactions in the breast-fed baby cannot be excluded. Therefore metoclopramide is not recommended during breastfeeding. Discontinuation of metoclopramide in breastfeeding women should be considered.

4.7 Effects on ability to drive and use machines

All routes of administration

Metoclopramide may cause drowsiness, dizziness, dyskinesia and dystonias which could affect the vision and also interfere with the ability to drive and operate machinery.

4.8 Undesirable effects

All routes of administration

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: very common (**≥**1/10), common (**≥**1/100, <1/10), uncommon (**≥**1/1000, <1/100), rare (**≥**1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reactions
Blood and lymphatic system disorders		
	Not known	Methaemoglobinaemia, which could be related to NADH cytochrome b5 reductase deficiency, particularly in neonates (see section 4.4). Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing medicinal products
Cardiac disorders		
	Uncommon	Bradycardia, particularly with intravenous formulation
	Not known	Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia (see section 4.4); Atrioventricular block, Sinus arrest particularly with intravenous formulation; Electrocardiogram QT prolonged; Torsade de Pointes;
Endocrine disorders*		
	Uncommon	Amenorrhoea, Hyperprolactinaemia
	Rare	Galactorrhoea
	Not known	Gyneacomastia
Gastrointestinal disorders		

	Common	Diarrhoea
General disorders and administration site conditions		
	Common	Asthenia
Immune System disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulation
Nervous system disorders		
	Very common	Somnolence
	Common	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the drug) (see section 4.4), Parkinsonism, Akathisia
	Uncommon	Dystonia, Dyskinesia, Depressed level of consciousness
	Rare	Convulsion especially in epileptic patients
	Not known	Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients (see section 4.4), Neuroleptic malignant syndrome (see section 4.4)
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional State
Vascular disorder		
	Common	Hypotension, particularly with intravenous formulation
	Not known	Shock, syncope after injectable use, Acute hypertension in patients with phaechromocytoma (see section 4.3)

* Endocrine disorders during prolonged treatment in relation with hyperprolactinaemia (amenorrhoea, galactorrhoea, gynaecomastia).

The following reactions, sometimes associated, occur more frequently when high doses are used:

- Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the medicinal product, particularly in children and young adults (see section 4.4).

- Drowsiness, decreased level of consciousness, confusion, hallucination.

4.9 Overdose

All routes of administration

Symptoms
Extrapyramidal disorders, drowsiness, decreased level of consciousness, confusion, hallucination, and cardio-respiratory arrest may occur.

Management

In case of extrapyramidal symptoms related or not to overdose, the treatment is only symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian medicinal products in adults).
A symptomatic treatment and a continuous monitoring of the cardiovascular and respiratory functions should be carried out according to clinical status.

5.2 Pharmacokinetic properties

All routes of administration

Renal impairment The clearance of metoclopramide is reduced by up to 70% in patients with severe renal impairment, while the plasma elimination half-life is increased (approximately 10 hours for a creatinine clearance of 10-50 mL/minute and 15 hours for a creatinine clearance <10 mL/minute).

Hepatic impairment
In patients with cirrhosis of the liver, accumulation of metoclopramide has been observed, associated with a 50% reduction in plasma clearance.

Key Elements from the Package Leaflet (PL)

The information below is relevant for all routes of administration of metoclopramide unless otherwise specified. Please refer to the PLs for individual products for further information.

1. What Metoclopramide is and what it is used for

This product is an antiemetic. It contains a medicine called "metoclopramide". It works on a part of your brain that prevents you from feeling sick (nausea) or being sick (vomiting).

Parenteral route / IM-IV

Adult population
Metoclopramide 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

Paediatric population
Metoclopramide is used in children (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

Oral route

Adult population
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.

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

2. What you need to know before you are given Metoclopramide

Do not take Metoclopramide if:

For all formulations

- you are allergic to metoclopramide or any of the other ingredients of this medicine (listed in section 6)

- you have bleeding, obstruction or a tear in your stomach or gut.

- you have or may have a rare tumour of the adrenal gland, which sits near the kidney (pheochromocytoma)

- you have ever had involuntary muscle spasms (tardive dyskinesia), when you have been treated with a medicine

- you have epilepsy

- you have Parkinson's disease

- you are taking levodopa (a medicine for Parkinson's disease) or dopaminergic agonists (see below "Other medicines and Metoclopramide")
- you have ever had an abnormal blood pigment levels (methaemoglobinemia) or NADH cytochrome-b5 deficiency

Do not give Metoclopramide to a child less than 1 year of age (see below "Children and adolescents").

Do not take Metoclopramide if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before you take Metoclopramide.

Warnings and precautions

For all routes of administration

Talk to your doctor, pharmacist or nurse before taking Metoclopramide if:
- you have a history of abnormal heart beats (QT interval prolongation) or any other heart problems

- you have problems with the levels of salts in your blood, such as potassium, sodium and magnesium

- you are using other medicines known to affect the way your heart beats

- you have any neurological (brain) problems

- you have liver or kidney problems. The dose may be reduced (see section 3)

Your doctor may perform blood tests to check your blood pigment levels. In cases of abnormal levels (methaemoglobinemia), the treatment should be immediately and permanently stopped.

For immediate release oral formulations

You must wait at least 6 hours between each metoclopramide dose, even in case of vomiting and rejection of the dose, in order to avoid overdose.

For 15mg prolonged release oral formulations

You must wait at least 12 hours between each metoclopramide dose, even in case of vomiting and rejection of the dose, in order to avoid overdose.

For 30mg prolonged release oral formulations

You must wait at least 24 hours between each metoclopramide dose, even in case of vomiting and rejection of the dose, in order to avoid overdose.

Do not exceed 3-month treatment because of the risk of involuntary muscle spasms.

Children and adolescents

For all formulations

Uncontrollable movements (extrapyramidal disorders) may occur in children and young adults. This medicine must not be used in children below 1 year of age because of the increased risk of the uncontrollable movements (see above "Do not take Metoclopramide if").

Other medicines and Metoclopramide

For all routes of administration

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because some medicines can affect the way Metoclopramide works or Metoclopramide can affect how other medicines work. These medicines include the following:

- levodopa or other medicines used to treat Parkinson's disease (see above "Do not take Metoclopramide if")

- anticholinergics (medicines used to relieve stomach cramps or spasms)

- morphine derivatives (medicines used to treat severe pain)

- sedative medicines

- any medicines used to treat mental health problems

- digoxin (medicine used to treat heart failure)

- cyclosporine (medicine used to treat certain problems with the immune system)

- mivacurium and suxamethonium (medicines used to relax muscles)

- fluoxetine and paroxetine (medicine used to treat depression)

Metoclopramide with alcohol

For all routes of administration

Alcohol should not be consumed during treatment with metoclopramide because it increases the sedative effect of Metoclopramide.

Pregnancy, breast-feeding
For all routes of administration

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before being given this medicine. If necessary, Metoclopramide may be taken during pregnancy. Your doctor will decide whether or not you should be given this medicine.
Metoclopramide is not recommended if you are breast-feeding because metoclopramide passes into breast milk and may affect your baby.

Driving and using machines

For all routes of administration

You may feel drowsy, dizzy or have uncontrollable twitching, jerking or writhing movements and unusual muscle tone causing distortion of the body after taking Metoclopramide. This may affect your vision and also interfere with your ability to drive and use machines.

3. How to take Metoclopramide

Parenteral route

The medicine will normally be given to you by a doctor or a nurse. It will be given as a slow injection into a vein (over at least 3 minutes) or by injection into a muscle.
In adults patients

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 prevention: a single dose of 10mg is recommended.

All indications (paediatric patients aged 1-18 years)
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.

Dosing table Age	Body Weight	Dose	Frequency
1-3 years	10-14 kg	1 mg	Up to 3 times daily
3-5 years	15-19 kg	2 mg	Up to 3 times daily
5-9 years	20-29 kg	2.5 mg	Up to 3 times daily
9-18 years	30-60 kg	5 mg	Up to 3 times daily
15-18 years	Over 60kg	10 mg	Up to 3 times daily

Device / instruction for use

You should not take this medicine for more than 5 days to prevent delayed nausea and vomiting that may occur after chemotherapy.

For tablets/capsules/granules

Appropriate additional information regarding posologies adaptation should be implemented in the SmPC depending on the strength of the formulations

For formulations which cannot be used to administer a 5mg dose

Metoclopramide is not suitable for use in children weighing less than 61 kg.

Other pharmaceutical forms/strengths may be more appropriate for administration.

For formulations which can be used to administer a 5mg dose

Metoclopramide is not suitable for use in children weighing less than 30 kg.

Other pharmaceutical forms/strengths may be more appropriate for administration.

All routes of administration

Method of administration

For immediate release oral formulations

You must wait at least 6 hours between each metoclopramide dose, even in case of vomiting and rejection of the dose, in order to avoid overdose.

For 15mg prolonged release oral formulations
You must wait at least 12 hours between each metoclopramide dose, even in case of vomiting and rejection of the dose, in order to avoid overdose.

For 30mg prolonged release oral formulations
You must wait at least 24 hours between each metoclopramide dose, even in case of vomiting and rejection of the dose, in order to avoid overdose.

All routes of administration

Older people

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

Appropriate additional information regarding posologies adaptation should be implemented in the PIL depending on the formulations:

<Other pharmaceutical forms/strengths may be more appropriate for administration>

<This formulation is not suitable for administration>

Adults with kidney problems

Talk to your doctor if you have kidney problems. The dose should be reduced if you have moderate or severe kidney problems.

Adults with liver problems

Talk to your doctor if you have liver problems. The dose should be reduced if you have severe liver problems.

Children and adolescents

Metoclopramide must not be used in children aged less than 1 year (see section 2).

For all routes of administration

If you take more Metoclopramide than you should

Contact your doctor or pharmacist straight away. You may experience uncontrollable movements (extrapyramidal disorders), feel drowsy, have some troubles of consciousness, be confused, have hallucination and heart problems. You doctor may prescribe you a treatment for these signs if necessary.

For all routes of administration

If you forget to take Metoclopramide

Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

For all formulations

Stop the treatment and talk straight away to your doctor, pharmacist or nurse if you experience one of the following signs while having this medicine:

- uncontrollable movements (often involving head or neck). These may occur in children or young adults and particularly when high doses are used. These signs usually occur at the beginning of treatment and may even occur after one single administration. These movements will stop when when treated appropriately.
- high fever, high blood pressure, convulsions, sweating, production of saliva. These may be signs of a condition called neuroleptic malignant syndrome.
- Itching or skin rashes, swelling of the face, lips or throat, difficulty in breathing. These may be signs of an allergic reaction, which may be severe.

Very common (may affect more than 1 in 10 people)

- feeling drowsy.

Common (may affect up to 1 in 10 people)

- depression
- uncontrollable movements such as tics, shaking, twisting movements or muscle contracture (stiffness, rigidity)
- symptoms similar to Parkinson disease (rigidity, tremor)

- feel restless
- blood pressure decrease (particularly with intravenous route)
- diarrhoea
- feeling weak.

Uncommon (may affect up to 1 in 100 people)
- raised levels of a hormone called prolactin in the blood which may cause: milk production in men, and women who are not breast-feeding
- irregular periods
- hallucination
- decreased level of consciousness
- slow heartbeat (particularly with intravenous route)
- allergy

Rare (may affect up to 1 in 1,000 people)
- confusional state
- convulsion (especially in patients with epilepsy).

Not known (frequency cannot be estimated from the available data)
- abnormal blood pigment levels: which may change the colour of your skin
- abnormal development of breasts (gynaecomastia)
- involuntary muscle spasms after prolonged use, particularly in elderly patients
- high fever, high blood pressure, convulsions, sweating, production of saliva. These may be signs of a condition called neuroleptic malignant syndrome
- changes in heart beat, which may be shown on an ECG test
- cardiac arrest (particularly with injection route)
- shock (severe decrease of heart pressure) (particularly with injection route)
- fainting (particularly with intravenous route)
- allergic reaction which may be severe (particularly with intravenous route)
- very high blood pressure.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

Annex 3

This information is being provided jointly by the Marketing Authorisation holders listed below. Contact details are provided if you wish to request further information:

Company name and address	Product name	Contact details
Accord Healthcare Ltd.	Metoclopramide Hydrochloride 10 mg tablets	Sage House 319, Pinner Road, North Harrow, Middlesex HA1 4HF United Kingdom uk@accord-healthcare.com
Actavis UK Limited	Metoclopramide Tablets BP 10mg	Whiddon Valley, Barnstaple, North Devon, EX32 8NS, United Kingdom Medinfo@actavis.co.uk;
Amdipharm Mercury Company Limited (Formerly Amdipharm Plc and Mercury Pharma International Ltd)	Maxolon SR Maxolon Tablets 10mg Maxolon Injection 5mg/ml Maxolon High Dose 100mg/20ml Metoclopramide 5mg/ml solution for injection	Capital House, 1st Floor, 85 King William Street, London, EC4N 7BL, United Kingdom medicalinformation@amcolimited.com (T) +44 (0) 208 588 9131 (F) +44 (0) 208 588 9200
Crescent Pharma Limited	Metoclopramide 10mg Tablets	Units 3 & 4 Quidhampton Business Units Polhampton Lane, Overton Hampshire RG25 3ED United Kingdom info@crescentpharma.com
Hameln Pharmaceuticals Limited	Metoclopramide Injection BP 5mg/ml	Nexus Gloucester Business Park Gloucester GL3 4AG United Kingdom drugsafety@hameln.co.uk
Teva UK Limited	Primperan; Metoclopramide Tablets BP 10mg	Brampton Road Hampden Park, Eastbourne East Sussex BN22 9AG United Kingdom medinfo@tevauk.com