SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Maxolon ® SR

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Metoclopramide Hydrochloride equivalent to 15mg of the anhydrous substance.

Excipient with known effect
Sucrose- 176.821mg per capsule

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Colourless, transparent capsules, overprinted 'Maxolon SR 15', containing white sustained release microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult population
Maxolon SR 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
Maxolon SR 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

Posology:

Adults
The recommended single dose is 15 mg, repeated up to twice daily.

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

Paediatric population

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

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

Capsules 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.

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

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).

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).

4.3 Contraindications

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

'Maxolon' should not be used during the first three to four days following operations such as pyloroplasty or gut anastomosis as vigorous muscular contractions may not help healing.

- 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

Precautions:
If vomiting persists the patient should be reassessed to exclude the possibility of an underlying disorder e.g. cerebral irritation.

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.

Metoclopramide may cause elevation of serum prolactin levels.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Care should be exercised when using Maxolon in patients with a history of atopy (including asthma) or porphyria.

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).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.
'Maxolon' may reduce plasma concentrations of atovaquone.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no malformative nor feto/neonatal toxicity of Metoclopramide hydrochloride. 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.

Breast-feeding
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.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Maxolon has moderate influence on the ability to drive and use machines.
Maxolon 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

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: Very common (≥1/10), Common (≥1/100to <1/10), Uncommon (≥1/1,000to <1/100), Rare (≥1/10,000to <1/1,000), Very rare (<1/10,000), 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
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulation
Endocrine disorders*		
	Uncommon	Amenorrhoea, Hyperprolactinaemia,
	Rare	Galactorrhoea
	Not known	Gynaecomastia
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
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 (including visual disturbances and oculogyric crisis), 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)
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;
Vascular disorders		
	Common:	Hypotension, particularly with intravenous formulation
	Not known	Shock, syncope after injectable use Acute hypertension in patients with phaeochromocytoma (see section 4.3) Transient increase in blood pressure
Gastrointestinal disorders		
	Common	Diarrhoea
General disorders and administration site conditions		
	Common	Asthenia

* 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents stimulating gastro-intestinal motility,

ATC code: A03FA01

Mechanism of action

The action of metoclopramide is closely associated with parasympathetic nervous control of the upper gastro-intestinal tract, where it has the effect of encouraging normal peristaltic action. This provides for a fundamental approach to the control of those conditions where disturbed gastro-intestinal motility is a common underlying factor.

5.2 Pharmacokinetic properties

The following pharmacokinetic parameters for MAXOLON SR after a single administration have been established.

C_{max}	102.5 nmol/l
T_{max}	4.5 hours
AUC	1514.25 nmol.hr/l
$t_{½}$ (elim)	7.04 hours
$C_{12\ hrs}$	54.75 nmol/l

On repeated administration the following parameters have been established.

C_{max}	188 nmol/l
C_{min}	109 nmol/l

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.

5.3 Preclinical safety data

No relevant information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Maize starch
Dibutyl phthalate
Talc
Polymethacrylates
Gelatin
Black iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Polypropylene containers: 3 years

Blister packs: 2 years

6.4 Special precautions for storage

Protect from direct light.

6.5 Nature and contents of container

All pack sizes (8, 14 or 56 capsules) are available in the following packs :

PVC blister (300 microns) backed with aluminium foil (20 microns). The underside of the foil is coated with vinyl based lacquer.

PVC (200 microns) PVDC (60gsm) blister.

Polypropylene containers with polyethylene caps.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm UK Limited,

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London, EC2M 1QS,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0047

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08/04/2024