

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Metoclopramide Actavis 5, film coated tablets, 5 mg

Metoclopramide Actavis 10, film coated tablets, 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg or 10 mg of metoclopramide hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Metoclopramide Actavis 5: White to off-white, circular, biconvex film coated tablets plain on both sides.

Metoclopramide Actavis 10: White to off-white, circular, biconvex film coated tablets with breakline on both sides. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults (20 years and over)

Digestive Disorders

Metoclopramide Actavis restores normal co-ordination and tone to the upper digestive tract and relieves symptoms of gastroduodenal dysfunction including:

- Dyspepsia
- Heartburn
- Flatulence
- Sickness
- Regurgitation of bile
- Pain.

These symptoms may be associated with such conditions as:

- Peptic ulcer
- Duodenitis
- Reflux oesophagitis
- Gastritis
- Hiatus hernia
- Cholelithiasis and post-cholecystectomy dyspepsia.

Nausea and Vomiting

Metoclopramide Actavis is indicated in the treatment of nausea and vomiting associated with:

- Gastrointestinal disorders
- Cyclical vomiting
- Intolerance to cytotoxic medicines
- Congestive heart failure
- Deep x-ray or cobalt therapy
- Post-anaesthetic vomiting.

Migraine

Metoclopramide Actavis relieves symptoms of nausea and vomiting, and overcomes gastric stasis associated with attacks of migraine. This improvement in gastric emptying assists the absorption of concurrently administered oral antimigraine therapy (e.g. paracetamol) which may otherwise be impaired in such patients.

Post-Operative Conditions

- Post-operative gastric hypotonia
- Post-vagotomy syndrome.

Metoclopramide Actavis promotes normal gastric emptying and restores motility in vagotomised patients, and where postoperative symptoms suggest gastroduodenal dysfunction.

Diagnostic Procedures

- Radiology
- Duodenal intubation.

Metoclopramide speeds up the passage of a barium meal by decreasing gastric emptying time, co-ordinating peristalsis and dilating the duodenal bulb. Metoclopramide also facilitates duodenal intubation procedures.

Young Adults and Children

The use of Metoclopramide Actavis in patients under 20 years should be restricted to the following and used only as second line therapy:

- Severe intractable vomiting of known cause
- Vomiting associated with radiotherapy and intolerance to cytotoxic medicines
- As an aid to gastrointestinal intubation
- As part of the premedication before surgical procedures.

4.2 Dose and method of administration

Dose

The dosage recommendations given below should be strictly adhered to if side effects of the dystonic type are to be avoided. It should be noted that total daily dosage of Metoclopramide Actavis, especially for children and young adults, should not normally exceed 0.5 mg/kg body weight or 30 mg daily. Maximum recommended treatment duration is 5 days in all age groups.

Adults

The recommended dosage for adults, 20 years and older, is 10 mg three times daily.

For patients less than 60kg, see Table 1.

Special populations

Elderly population

As for adults. To avoid adverse reactions adhere strictly to dosage recommendations and where prolonged therapy is considered necessary, patients should be regularly reviewed.

Renal and hepatic impairment

In patients with clinically significant degrees of renal or hepatic impairment, therapy should be at reduced dosage. Metoclopramide is metabolised in the liver and the predominant route of elimination of metoclopramide and its metabolites is via the kidney.

Young Adults and Children

Metoclopramide Actavis should only be used after careful examination to avoid masking an underlying disorder e.g. cerebral irritation. In the treatment of this group attention should be given primarily to body weight and treatment should begin at the lower dosage where stated. Metoclopramide Actavis should be used as second line therapy in these patients.

Young Adults:	15 – 19 years	60kg & over	10 mg three times daily
		30kg – 59kg	5 mg three times daily

Diagnostic Indications

A single dose of Metoclopramide Actavis may be given 5-10 minutes before the examination. Subject to body weight considerations (see above) the following dosages are recommended:

Adults:	20 years and over	10 mg – 20 mg
Young adults:	15 – 19 years	10 mg

Method of administration

Metoclopramide Actavis should not be used in children under the age of 15 years since the product range does not have the strengths or dose forms required to deliver the smaller doses required for this age group. Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

4.3 Contraindications

Metoclopramide Actavis should not be used whenever stimulation of gastrointestinal motility might be dangerous, for example, in the presence of gastrointestinal haemorrhage, mechanical obstruction, or perforation.

Metoclopramide Actavis is contraindicated in patients with phaeochromocytoma because the medicine may cause a hypertensive crisis, probably due to release of catecholamines from the tumour. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide Actavis is contraindicated in patients with known hypersensitivity or intolerance to the medicine.

Metoclopramide Actavis is contraindicated:

- patients with porphyria
- metoclopramide should not be used in patients with epilepsy since it may increase the frequency and severity of seizures.
- metoclopramide should not be administered to patients receiving other medicines which are likely to cause extrapyramidal reactions, since the frequency and severity of extrapyramidal reactions may be increased.

4.4 Special warnings and precautions for use

Dystonic reactions

These occur in approximately 1% of patients given metoclopramide. These occur more frequently in children and young adults and may occur after a single dose.

Persistent tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or may appear after treatment has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterised by rhythmical involuntary movement of the tongue, face, mouth or jaw (eg.

protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movement of extremities. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome.

Although the risk of tardive dyskinesia with metoclopramide has not been extensively studied, one published study reported a tardive dyskinesia prevalence of 20% among patients treated for at least 3 months. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Metoclopramide therapy should routinely be discontinued in patients who develop signs or symptoms of tardive dyskinesia. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and, if the medications stopped at that time, the syndrome may not develop. Tardive dyskinesia may remit partially or completely within several weeks to months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore metoclopramide should not be used for the symptomatic control of tardive dyskinesia. Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all rare cases where the therapeutic benefit is thought to outweigh the risk to the patient of developing tardive dyskinesia.

Care should be exercised in patients being treated with other centrally active medications.

Since extrapyramidal symptoms may occur with both metoclopramide and neuroleptics such as phenothiazines, care should be exercised in the event of both medicines being prescribed concurrently.

Neuroleptic Malignant Syndrome

This has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy (see Undesirable Effects).

Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia, and impotence have been reported with prolactin elevating medicines, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin stimulating neuroleptic medications.

Neither clinical studies nor epidemiological studies conducted to date, however, have shown an association between chronic administration of these medicines and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

The frequency and severity of seizures or extrapyramidal reactions may be increased in epileptic patients given metoclopramide.

Following operations such as pyloroplasty or gut anastomosis, metoclopramide therapy should be withheld for three or four days as vigorous muscular contractions may not help healing.

Special care should be taken in cases of severe renal insufficiency (see Dose and method of administration).

The symptomatic relief provided by metoclopramide may delay recognition of serious disease. It should not be prescribed until diagnosis has been established, and should not be substituted for appropriate investigation of the patient's symptoms.

Metoclopramide should not be given to children unless a clear indication has been established for its use, because of the higher incidence of adverse reactions in this age group.

If vomiting persists, the patient should be reassessed to exclude the possibility of an underlying disorder eg. cerebral irritation.

Patients should be cautioned about engaging in activities requiring mental alertness for a few hours after the medicine has been administered.

Metoclopramide induced depression has been reported in patients without a prior history of depression. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Metoclopramide should be used with caution in patients with hypertension as intravenously administered metoclopramide has been shown to release catecholamines.

Metoclopramide can exacerbate Parkinsonian symptoms; therefore it should be used with caution, if at all, in patients with Parkinsonian syndrome.

4.5 Interaction with other medicines and other forms of interaction

The effects of metoclopramide on gastrointestinal motility are antagonised by anticholinergic medicines and narcotic analgesics.

Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics or tranquillisers.

Since metoclopramide accelerates abnormally slow gastric and small bowel peristaltic activity, it may change absorption of orally administered medicines.

The absorption of medicines from the small bowel may be accelerated (eg. paracetamol, tetracycline, L-dopa), whereas absorption of medicines from the stomach may be diminished (eg. digoxin).

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category A)

Adequate human data on use during pregnancy are not available.

Use in lactation

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequent adverse reactions to metoclopramide are restlessness, drowsiness, fatigue and lassitude, which occur in approximately 10% of patients.

Less frequently, insomnia, headache, dizziness, nausea, or bowel disturbances may occur. Rare (less than 1 in 1,000) cases of acute depression have been reported. Anxiety or agitation may occur.

A single instance of supraventricular tachycardia following intramuscular administration has been reported. There have been very rare (less than 1 in 10,000) cases of abnormalities of cardiac conduction (such as bradycardia and heart block) in association with intravenous metoclopramide.

Raised serum prolactin levels have been observed during metoclopramide therapy: this may result in galactorrhoea, irregular periods and gynecomastia.

Although uncommon at normal dosage, various extrapyramidal reactions to metoclopramide, usually of the dystonic type, have been reported. Reactions include: spasm of the facial muscles, trismus, rhythmic protrusion of the tongue, a bulbar type of speech, spasm of the extraocular muscles including oculogyric crises, unnatural positioning of the head and shoulders and opisthotonos. There may be a generalised increase in muscle tone. The majority of reactions occur within 36 hours of starting treatment and the effects usually disappear within 24 hours of withdrawal of the medicine, however, close observation is required and in cases of more severe reactions, an antiparkinson medication such as benzotropine or an anticholinergic antihistamine such as diphenhydramine should be given.

Tardive dyskinesia, which may be persistent, has been reported particularly in elderly patients undergoing long-term therapy with metoclopramide.

Very rare (less than 1 in 10,000) occurrences of the Neuroleptic Malignant Syndrome have been reported. This syndrome is potentially fatal and comprises hyperpyrexia, altered consciousness, muscle rigidity, autonomic instability and elevated levels of CPK and must be treated urgently (recognised treatments include dantrolene and bromocriptine). Metoclopramide Actavis should be stopped immediately if this syndrome occurs.

Methaemoglobinaemia has also been reported.

Hypersensitive reactions, Parkinsonian symptoms including tremor, rigidity, bradykinesia and akinesia, respiratory failure, urinary incontinence, depression, very rare reports of abnormalities of cardiac conduction (bradycardia, asystole, heart block, sinus arrest and cardiac arrest) have been reported following intravenous administration.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Extrapyramidal side effects are the most frequently reported adverse reactions to overdose. Very rarely AV block has been observed. Management of overdose consists of close observation and supportive therapy. Antiparkinson and antihistamine/anticholinergic medicines such as diphenhydramine hydrochloride have effectively controlled extrapyramidal reactions. Haemodialysis appears ineffective in removing metoclopramide. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of the medicine.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders; Propulsives, ATC code: A03FA01

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitise tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic medicines.

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum

resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower oesophageal sphincter. It has little, if any effect on the motility of the colon or gall bladder.

Metoclopramide has dopamine antagonist activity. Like the phenothiazines and related medicines, which are also dopamine antagonists, metoclopramide produces sedation and may produce extra-pyramidal reactions (see Special warnings and precautions for use).

Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels.

5.2 Pharmacokinetic properties

The onset of pharmacological action is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

There is marked variability in peak plasma concentrations of metoclopramide after oral administration, which appears to be due to interindividual differences in first-pass metabolism. Plasma protein binding is 13 to 22%. About 80% of the drug is excreted in the urine in the first 24 hours, approximately half as the glucuronide and sulfate conjugates and half as unchanged drug. Elimination half-life varies in different studies from 2.5 to 5 hours. Impaired renal function results in reduced clearance of metoclopramide and an increased half-life (15 hours).

5.3 Preclinical safety data

None.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch, microcrystalline cellulose, maize starch, colloidal anhydrous silica, stearic acid, hypromellose, macrogol 6000, titanium dioxide and purified talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

PVC/Aluminium foil blister strips. Pack sizes of 100 or 500 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

22 May 2014

10. DATE OF REVISION OF THE TEXT

22 May 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Update to the SPC-style format
4.1 & 4.2	Updated to include maximum dose in mg and treatment duration of 5 days.
8.	Sponsor company name and address details updated