1. NAME OF MEDICINAL PRODUCT
Cerucal injections

2. QUALITATIVE UND QUANTITATIVE COMPOSITION
Active substance: metoclopramide hydrochloride 10 mg
For a complete list of other ingredients see Section 6.1.

3. PHARMACEUTICAL FORM
Injection solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
- motility disturbances of the upper gastro-intestinal tract
- nausea, retching and vomiting (with liver and kidney diseases, skull and brain injuries, migraine and drug intolerance)
- diabetic gastroparesis
- to facilitate probing of the duodenum and jejunum, to accelerate emptying of the stomach and for small bowel follow-through X-ray examination of the stomach and small bowel.

4.2 Posology and method of administration

In case of motility disturbances of the upper gastro-intestinal tract, nausea, retching and vomiting, diabetic gastroparesis

Adults and young people over 14 years:
Adults and young people are given 1 ampoule of Metoclopramide 1 – 3 times daily (corresponding to 10 mg Metoclopramide 1 – 3 times daily).

Children:
The exact dosage depends on the body weight of the child:
The recommended single dose for children over 2 years up to 14 years of age is 0.1 mg of metoclopramide/kg BW (corresponding to 0.02 ml Metoclopramide injection solution /kg BW), the maximum daily dose is 0.5 mg of metoclopramide/kg BW.

Recommended dosage:

<table>
<thead>
<tr>
<th>body weight (kg)</th>
<th>single dose (mg / ml)</th>
<th>max. daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>5 /1,0</td>
<td>25</td>
</tr>
<tr>
<td>30</td>
<td>3 /0,6 ml</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>2 /0,4 ml</td>
<td>10</td>
</tr>
</tbody>
</table>
For examination of the upper gastro-intestinal tract:

Adults and young people over 14 years:
Adults and young people over 14 years of age are given 1 - 2 ampoules of Metoclopramide (10 – 20 mg metoclopramide) slowly (within 1 – 2 minutes) by the intravenous route about 10 minutes before the examination starts.

Children:
Children over 2 years up to 14 years of age are given 0,1 mg metoclopramide/KG BW slowly within 1 - 2 minutes by intravenous injection about 10 minutes before the examination starts.

With a restricted renal function the dose has to be adapted to the functional disturbance. The following figures hold for adults (no study results are as yet available for children):

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose of metoclopramide</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 10 ml/min</td>
<td>1 ampoule once a day</td>
</tr>
<tr>
<td></td>
<td>(10 mg Metoclopramide)</td>
</tr>
<tr>
<td>11 to 60 ml/min</td>
<td>1 ampoule once a day</td>
</tr>
<tr>
<td></td>
<td>(10 mg Metoclopramide) and ½ ampoule once a day</td>
</tr>
<tr>
<td></td>
<td>(5 mg Metoclopramide)</td>
</tr>
</tbody>
</table>

For patients with a severe hepatic insufficiency with ascites (dropsy of the belly) the dose should be reduced by half because of the prolonged elimination half-life.

Method and duration of administration
The injection solution is given by the intramuscular route or slowly by the intravenous route. The duration of treatment depends on the basic disease. 4 - 6 weeks are generally sufficient. A long term treatment of up to 6 months is possible in exceptional cases.

Note:
On prolonged treatment with Metoclopramide the risk of the occurrence of movement disorders is increased (c.f. “Side effects”).

4.3 Contraindications

- hypersensitivity to the active ingredient metoclopramide or any of the other ingredients
- phaeochromocytoma
- prolactin-dependent tumours
- mechanical ileus
- intestinal perforation
- haemorrhages in the gastro-intestinal region
- epilepsy
- extrapyramidal motor disturbances
- first 3 months of pregnancy and during lactation
The administration of drugs that contain metoclopramide is not indicated for infants and small children under 2 years of age.
Metoclopramide injections should be administered to children from 2 to 14 years of age only on the basis of an exact diagnosis.
In the treatment of patients suffering from hepatic insufficiency and patients with an impaired renal function, the dose should be adapted to the dysfunction since elimination is delayed (see Section 4.2 "Posology and method of administration").

4.4 Special warnings and precautions

As Metoclopramide injection solution contains sodium sulphite, it must not be used on asthmatics with a hypersensitivity to sulphite.
Metoclopramide injections contain Sodium but less than 1 mmol (23 mg) sodium per 2 ml injection solution.
Risk groups
- Pregnancy: c.f. point 4.6.
- Patients under 30 years of age have a stronger tendency to develop dystonic-dyskinetic motor disturbances when taking metoclopramide.
- In elderly patients parkinsonism appears frequently.
- For patients with a restricted renal function the dose has to be adapted to the functional disturbance.

4.5 Interactions with other medicinal products and other forms of interaction

Metoclopramide may interfere with the absorption of other substances. It may, for example, reduce the absorption of digoxin and cimetidine and accelerate / increase that of levodopa, paracetamol, various antibiotics (such as tetracycline, pivampicillin), lithium and alcohol. The combined administration of Metoclopramide and lithium may cause increased lithium plasma levels.

Anticholinergics may reduce the efficacy of Metoclopramide injections.

The combination of Metoclopramide injections with neuroleptics (such as phenothiazines, thioxanthene derivatives, butyrophenones) may trigger the increased occurrence of extrapyramidal disorders (such as spasmodic symptoms in the region of the head, neck and shoulders).

A combination with serotonin re-uptake inhibitors may also lead to an increase in extrapyramidal symptoms, including the occurrence of a serotonin syndrome.

The action of succinylcholine may be prolonged by Metoclopramide inject.

Special note:
Sodium sulphite is a very reactive compound. It must therefore be expected that when administered together with the preparation, thiamin (vitamin B1) will be degraded.

4.6 Fertility, pregnancy and lactation
Metoclopramide should not be used during the first 3 months of pregnancy and during lactation, as the available studies are insufficient. In the second and third trimesters of pregnancy accurate diagnosis is imperative for the use of metoclopramide.

4.7 Effects on the ability to drive and to operate machines

Even if used as intended, this drug may change the patients’ reactivity to such an extent as to impair their ability to drive or to operate machines. This risk is heightened in conjunction with alcohol and sedative drugs.

4.8 Undesirable effects

The assessment of side effects is based on the following rates of occurrence: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

**Blood and lymphatic system disorders**
*Very rare:* methaemoglobinaemia, sulphaemoglobinaemia

**Endocrine disorders**
*Not known:* hyperprolactinemia

**Psychiatric disorders**
*Very rare:* depression
*Not known:* anxiety, restlessness

**Nervous system disorders**
*Rare:* tardive dyskinesia, parkinsonism (tremor, rigor, akinesia)
*Very rare:* neuroleptic malignant syndrome, dyskinetic syndrome (Symptoms include spasm of head and neck muscles, trismus, rhythmic protrusion of the tongue, abnormal positioning of the head and shoulders. There may also be a generalised increase in muscle tone.)
*Not known:* headache, vertigo

**Gastrointestinal disorders**
*Rare:* diarrhoea;
*Not known:* mouth dryness

**Skin and subcutaneous tissue disorders**
*Uncommon:* skin rash

**Reproductive system and breast disorders**
*Not known:* gynaecomastia, galactorrhoea, amenorrhoea

**General disorders and administration site conditions**
*Not known:* tiredness; After intravenous injection, lowering of the blood pressure may be observed. Highly dosed intravenous administration of metoclopramide may cause an increase in blood pressure in isolated cases. Furthermore, there have been single reports on the occurrence of cardiac
arrhythmias such as supraventricular extrasystoles, ventricular extrasystoles, tachycardia and bradycardia sometimes resulting in cardiac arrest after parenteral administration of metoclopramide. Young people and patients with serious renal insufficiency and hence a restricted elimination of metoclopramide have to be attentively watched for side effects. If side effects occur, the treatment has to be stopped at once.

**Special note:**
Because of the sodium sulphite contained in Metoclopramide inject, there may be isolated cases of hypersensitivity reactions, especially among asthmatics, which may show themselves as nausea, diarrhoea, wheezy breathing, acute asthmatic attacks, disturbances of consciousness or shock. The course which these reactions take may differ widely and may even lead to life-endangering situations.

**4.9 Overdose**

*Symptoms of an overdose*
Somnolence, confusion, irritability, restlessness / increase in restlessness, convulsions, extrapyramidal motor disturbances, disturbances of the cardiovascular function with bradycardia and a rise / drop in blood pressure. Isolated cases of methaemoglobinaemia have been reported.

*Therapeutic measures to treat an overdose*
Antidote: Extrapyramidal symptoms disappear after slow i.v. administration of biperiden. If metoclopramide has been taken in large doses, it may be removed from the gastro-intestinal tract by a gastric lavage or by giving the patient medicinal charcoal and sodium sulphate. The vital functions should be watched until the symptoms have disappeared.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: procaine amide derivative with antiemetic properties as well as properties facilitating gastro-intestinal motility.
ATC Code: A03FA01

Metoclopramide is a central dopamine antagonist and also shows a peripheral cholinergic activity. There are two main effects to be distinguished:
1. an antiemetic effect, and
2. accelerated gastric emptying and small-bowel passage.
The antiemetic effect is caused by action on a central point on the brain stem (chemoreceptors – the trigger zone of the vomiting centre), probably by inhibiting dopaminergic neurons. The increase in motility is also, in part, controlled by superior centres, but a peripheral action mechanism plays a part as well by activating postganglionic cholinergic receptors and possibly inhibiting dopaminergic receptors in the stomach and the small intestine.

The undesirable effects consist mainly in extrapyramidal symptoms (involuntary spasmodic movements) on the basis of the dopamine-receptor-blocking action mechanism of metoclopramide in the central nervous system.
Prolonged treatment with metoclopramide may cause a rise in the serum prolactin concentration as the dopaminergic inhibition of prolactin secretion does not take place. Galactorrhoea and disturbances of the menstrual cycle have been described for women and gynaecomastia for men, but these symptoms disappear when the medication is discontinued.

5.2 Pharmacokinetic properties

After intravenous administration, rapid initial distribution of metoclopramide takes place. The maximum plasma concentrations after oral administration may vary widely. This is attributed to the interindividually variable first-pass metabolism of metoclopramide. Values between 2.6 and 4.6 hours were determined for the elimination half-life. Only an insignificant part of metoclopramide is bound to plasma proteins. The distribution volume ranges from 2.2 to 3.4 l/kg.

Metoclopramide passes through the blood-brain barrier into the mother’s milk. Part of it (about 20 per cent) is excreted unchanged through the kidney, the rest after metabolic degradation in the liver in conjugation with glucuronic or sulphuric acid.

5.3 Preclinical safety data

Acute toxicity

Acute toxicity was studied in various animal species (mice, rats, dogs). The intoxication symptoms are listed in Section 4.9 "Overdose".

Chronic toxicity

After subchronic and chronic administration of oral and intravenous doses, all animals showed corresponding intoxication symptoms: for dogs and rabbits they included a reduced food intake, diminished gain in body weight, diarrhoea, leucocytosis and anaemia, an increase in LDH and AP, sedation, anorexia; for rats an increase in SGOT, SGPT and total bilirubin. After chronic administration to rats and dogs, the lowest toxic dose amounted to between 11 and 35 mg/kg; the lethal dose range is expected to lie between 35 and 115 mg/kg, orally given. For dogs the lowest toxic dose ranged from 6 to 18 mg/kg i.v., for rabbits from 2 to 10 mg/kg i.v.

Mutagenic and tumourigenic potentials

Metoclopramide was not subjected to a full mutagenicity test. Mutagenicity studies of metoclopramide conducted on 3 bacterial strains (salmonella) did not produce evidence of any mutagenic properties. In a 77-week study of the tumourigenic potential of rats, oral doses 40 times as large as the human therapeutic dose were used. Apart from an increase in the prolactin level, no conspicuous results were obtained. Nor did clinical or epidemiological studies furnish evidence of a correlation between the chronic application of prolactin-stimulating substances and mamma tumourigenesis.

Reproduction toxicity

Reproduction studies were conducted with three animal species (mice, rats and rabbits). No indications of teratogenic or embryotoxic properties were found even in the largest doses tested (116.2 / 200 mg/kg orally given). Dosages resulting in increased prolactin levels caused reversible disorders of spermatozoon formation in rats.
The effects of the administration of metoclopramide to humans during pregnancy were studied in about 200 mother-child pairs; about 130 of them were exposed to it in the first trimester of pregnancy. No adverse effects on the newborn children were detected, although the knowledge gained to date is not sufficient to rule out such effects with certainty. No reproduction toxicological studies of metoclopramide in combination with cytostatics are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium sulphite anhydrous,
Disodium edetate
Sodium chloride
Water for injections

6.2 Incompatibilities
Not applicable

6.3 Shelf life
5 years.

6.4 Special precautions for storage
Don’t store above 30°C. Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container
Five labeled ampoules of 2 ml each are packed into PVC blisters.
Two blisters and a leaflet are inserted into a carton box.

7. MARKETING AUTHORIZATION HOLDER
TEVA Pharmaceutical Industries LTD
5, Basel Street, P.O. Box 3190,
49131 Petach Tikva, Israel

Manufacturer:
Teva Pharmaceutical Works Private Limited Company
H-2100 Gödöllő, Táncsics Mihály út 82., Hungary

8. MARKETING AUTHORIZATION NUMBER
Not applicable

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION
Not applicable

10. LATEST UPDATE
Not applicable