SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Paramax 500mg/5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 500mg paracetamol with 5mg metoclopramide hydrochloride (calculated with reference to anhydrous substance).
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Adult population
Paramax is indicated for the symptomatic treatment of migraine

4.2 Posology and method of administration

Posology
Paramax should be taken at the first warning of an attack. If symptoms persist, further doses may be taken at four-hourly intervals. Total dosage in any 24-hour period should not exceed the quantity stated.

The dosage recommendations given below should be strictly adhered to if side-effects of the dystonic type are to be avoided.

<table>
<thead>
<tr>
<th>Usual Recommended Dosage (number of tablets)</th>
<th>Initial dose at first warning of attack</th>
<th>Maximum dosage in any 24-hour period</th>
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<tbody>
<tr>
<td>Adults (including elderly patients)</td>
<td>2</td>
<td>6</td>
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</table>

Treatment should not exceed 3 months due to the presence of metoclopramide (see also sections 4.4 and 4.8).
Paediatric population including adolescents
Use in children less than 1 year of age is contra-indicated due to increased risk of extrapyramidal disorders (see section 4.4). Use in children and adolescents between the ages of 1 and 18 years is not recommended.

Method of administration
For oral administration only.

4.3 Contraindications

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

Gastrointestinal haemorrhage, obstruction or perforation, since stimulation of gastrointestinal motility constitutes a risk in these situations.

History of neuroleptic or metoclopramide-induced tardive dyskinesia.

Confirmed epilepsy, since the frequency and severity of seizures may be increased.

Confirmed or suspected phaeochromocytoma, because of the risk of hypertensive crisis.

Combination with levodopa because of a mutual antagonism.

Metoclopramide should be not be used in the immediate post-operative period (up to 3-4 days) following pyloroplasty or gut anastomosis, as vigorous gastrointestinal contractions may adversely affect healing.

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

4.4 Special warnings and precautions for use
Patients should not take Paramax with any other paracetamol-containing products. Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with (non-cirrhotic) alcoholic liver disease. Due to the risk of tardive dyskinesia with metoclopramide treatment should not exceed 3 months (see also sections 4.2 and 4.8). Care should be exercised in the event of Paramax being prescribed concurrently with a phenothiazine since extra-pyramidal symptoms may occur with both products (see section 4.5).
Extrapyramidal disorders, (drowsiness, decreased level of consciousness, confusion and hallucination) may occur, particularly in children and young adults and/or when high doses are used (see section 4.8) These adverse reactions resolve completely after treatment discontinuation.

A symptomatic treatment of extrapyramidal reactions may be necessary (benzodiazepines in children and/or anticholinergic anti-parkinsonian drugs in adults).

If vomiting persists the patient should be re-assessed to exclude the possibility of an underlying disorder, e.g. cerebral irritation.

Care should be exercised in patients being treated with other centrally active drugs (see section 4.5).

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex with hyperthermia, muscle rigidity, extrapyramidal symptoms, altered mental status and autonomic dysfunction, may occur. The management of NMS should include

1) immediate discontinuation of the product,
2) intensive symptomatic treatment and medical monitoring, and
3) treatment of any concomitant serious medical problems for which specific treatments are available.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combination:

**Levodopa:** Levodopa and metoclopramide have a mutual antagonism (see section 4.3)

Combination to be avoided:

**Alcohol:** Alcohol potentiates the sedative effect of metoclopramide.

**Paracetamol** may potentiate the effects of alcohol. Therefore, the risk of sedation and the effects of alcohol may be increased when Paramax is taken with alcohol.

**Chloramphenicol:** Paracetamol may increase the elimination half-life of chloramphenicol. **Oral contraceptives:** Oral contraceptives may increase the rate of paracetamol clearance.

**Metoclopramide or domperidone:** The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.
Colestyramine: The speed of absorption of paracetamol may be reduced by colestyramine.
Warfarin and other coumarins: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

**Combination to be taken into account:**
Anticholinergics and morphine derivatives: Anticholinergics and morphine derivatives antagonise the effects of metoclopramide on the gastrointestinal motility.
CNS depressants (morphine derivatives, hypnotics, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related): Combination of CNS depressants with metoclopramide may result in potentiation of sedative effects.
Antipsychotics: Combination of antipsychotics with metoclopramide may result in potentiation of extrapyramidal effects.
Due to the promotion of gastric emptying and normal peristalsis (see section 5.1) caused by metoclopramide, the absorption of certain drugs may be modified:
- Digoxin: Metoclopramide decreases the gastric absorption of digoxin. Therefore, dose adjustment may be required.
- Ciclosporin: Metoclopramide increases ciclosporin bioavailability. Dose adjustment may be required. In one study, dosing requirements for ciclosporin were reduced by 20% when metoclopramide was administered concomitantly. To avoid toxicity, careful monitoring of ciclosporin plasma concentration in therefore required.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
Animal studies, carried out on the individual active components, have not demonstrated any teratogenic effect. These studies have not been carried out on the combination product. In the absence of a teratogenic effect in animals, a malformative effect in humans is not anticipated.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Metoclopramide: data on pregnant patients (>1000) indicate no malformative nor foeto/neonatal toxicity during the first trimester of pregnancy. A limited amount of data on pregnant patients (>300) indicates no neonatal toxicity in other trimesters. Animal studies do not indicate reproductive toxicity.

Exposure of pregnant women to the individual active components indicates no adverse effect on pregnancy or on the health of the foetus/new born child. To date, no epidemiological data are available for the combination product. Paramax should only be used during pregnancy when there are compelling reasons and like all drugs avoid
use in the first and second trimester unless the physician believes the benefits outweigh the risk. Thereafter, patients should follow the advice of their doctor regarding its use.

**Breastfeeding**
During lactation, metoclopramide and paracetamol are excreted in breast milk and adverse reactions in the breast-fed baby cannot be excluded. A decision should be made whether to discontinue breast-feeding or to abstain from Paramax treatment.

**4.7 Effects on ability to drive and use machines**
Paramax may cause drowsiness. The ability to drive vehicles or operate machinery can be impaired, particularly if Paramax is administered with CNS depressants or alcohol.

**4.8 Undesirable effects**

The information below lists reported adverse reactions, ranked using the following frequency classification:
- Very common (≥1/10);
- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);
- Rare (≥1/10,000 to <1/1,000);
- Very rare (<1/10,000), not known (cannot be estimated from the available data).

**Nervous system disorders**
The following reactions, sometimes associated, occur more frequently when high doses are used:
- Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia may increase following administration of a single dose particularly in children, young adults and the elderly (see section 4.4 Special warnings and precautions for use). Although, rarely, tardive dyskinesia may be irreversible.

The incidence of extrapyramidal symptoms in children and young adults may increase if the metoclopramide dosage exceeds 0.5mg/kg body weight/day.
Reactions include spasm of the facial muscles, trismus, rhythmic protrusion of the tongue, a bulbar type of speech, spasm of extra-ocular 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 drug. Should treatment of a dystonic reaction be required, a benzodiazepine or an anticholinergic anti-Parkinsonian drug may be used.
- Drowsiness, decreased level of consciousness, confusion, hallucination.

Other reactions may occur:
• Tardive dyskinesia, particularly in elderly patients and following or after prolonged treatment (see also section 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use)

• Seizures
• Neuroleptic malignant syndrome.

Gastrointestinal disorders
• Diarrhoea

Blood and Lymphatic system disorders
Metoclopramide may cause:
• Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency have been reported, particularly in neonates.
• Sulfaemoglobinemia, mainly with concomitant administration of high doses of sulfur-releasing drugs.
• Blood dyscrasias including thrombocytopenia and agranulocytosis,

Skin and subcutaneous disorders
Very rare cases of serious skin reactions such as Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption have been reported.

Psychiatric disorders
• Metoclopramide may cause dizziness, depression, restlessness, anxiety

Endocrine disorders
• Hyperprolactinaemia with (amenorrhea, galactorrhea, gynaecomastia).

General disorders and administration site conditions
• Very rarely hypersensitivity, including anaphylaxis has been reported.
• Asthenia.
• Skin rash

Cardiac and vascular disorders
• Hypotension.
• Bradycardia, heart block have been reported with metoclopramide, particularly the intravenous formulation.
• Transient increase in blood pressure (frequency not known)

Since extrapyramidal symptoms may occur with both metoclopramide and phenothiazines, care should be exercised in the event of both drugs being prescribed concurrently.
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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

If the patient:
- Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes.
- Regularly consumes ethanol in excess of recommended amounts.
- Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding and death.

Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage.

Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be
measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

**Metoclopramide**
Metoclopramide overdose may cause extrapyramidal disorders and drowsiness, decreased level of consciousness, confusion, hallucinations and convulsions.

Decreased level of consciousness, confusion, hallucinations resolve after metoclopramide withdrawal.

Treatment for extrapyramidal disorders caused by metoclopramide overdose is only symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian drugs in adults).

5.1 Pharmacodynamic properties

ATC code: N02B E51, Paracetamol, combinations excl. psycholeptics

The mechanism of action of metoclopramide in the gastrointestinal tract remains unclear and current hypotheses have been reviewed by Harrington et al (1983). It appears that metoclopramide has both central and local mechanisms of action; at the local level metoclopramide may have a direct effect on gastric muscle, stimulating contractility (Hay, 1975).

The addition of metoclopramide to paracetamol therapy for migraine has the additional benefit of combating the nausea and vomiting which are often experienced by migraine sufferers. The antiemetic activity of metoclopramide is probably mediated, at least in part, by blockade of dopamine receptors in the chemoreceptor trigger zone for vomiting (Harrington et al 1983).

5.2 Pharmacokinetic properties

Published data concerning the pharmacokinetics of Paramax is limited. In a study involving four healthy volunteers in which plasma paracetamol concentrations were compared following administration of Paramax tablets (1g paracetamol + 10mg metoclopramide), Panadol tablets (1g paracetamol) and Solpadeine effervescent tablets (1g paracetamol + 16mg codeine phosphate + 16mg caffeine), absorption of paracetamol from Paramax tablets was found not to differ significantly from absorption from Panadol or Solpadeine (Dougall et al, 1983).
Oral paracetamol is largely absorbed from the small intestine, the rate of absorption depending on the rate of gastric emptying (Heading et al., 1973; Clements et al., 1978).

Gastric emptying is often severely delayed during migraine attacks (Kreel, 1969); absorption of oral paracetamol has been shown to be delayed and impaired in patients during a migraine attack compared to when the same patients are headache free (Tokala and Neuvonen, 1984). Metoclopramide stimulates gastric emptying and has been shown to accelerate absorption of paracetamol (Nimmo et al., 1973 and Crome et al., 1981).

5.3 Preclinical safety data
Paracetamol and metoclopramide hydrochloride are well established drug substances and results of preclinical testing are well documented.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Gelatin
- Colloidal silica dioxide
- Magnesium stearate
- Microcrystalline cellulose

6.2 Incomaptibilities
Not applicable

6.3 Shelf life
3 years
Do not use after expiry date given on the label

6.4 Special precautions for storage
Store in the original container. Do not store above 25°C.
6.5 Nature and contents of container

PVC (250μm) / aluminium foil (aluminium (20μm) / PVC (15μm)) blister packs

Or

PVC (250μm) / PE (25μm) / PVDC (90 g/m²) aluminium foil (aluminium (20μm) / PVC (15μm)) blister packs.

Pack sizes: 30, 42, 100 or 108 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Winthrop Pharmaceuticals UK Limited
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Trading as: Zentiva, One Onslow Street, Guildford, Surrey, UK.

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07/11/2016