SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Migramax 900mg/10mg Powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients

<table>
<thead>
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<th>Per sachet</th>
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<tr>
<td>DL-lysine acetylsalicylate</td>
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<tr>
<td>equivalent to acetylsalicylic acid</td>
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<tr>
<td>Metoclopramide (INN) hydrochloride EP</td>
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<td>equivalent in terms of the anhydrous substance to</td>
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3 PHARMACEUTICAL FORM

Sachet containing powder for oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

**Adult population**
Migramax is indicated for the treatment of migraine-associated symptoms such as headache, nausea and vomiting.

4.2 Posology and method of administration

For oral administration only.

Migramax must be dissolved completely in some water before taking.

Renal and hepatic insufficiency
Caution should be exercised in significant renal or hepatic impairment. Metoclopramide is metabolised in the liver and eliminated mainly via the kidney. A dose reduction may be necessary.

**Adults (aged 18 years and older) and elderly:** One sachet should be taken at the first warning of a migraine attack. A second sachet may be taken two hours later if the symptoms have not resolved. Do not exceed three sachets in a 24 hour period.

**Paediatric population including adolescents**
Use in children less than 1 year of age is contraindicated (see section 4.3)
Use in children and adolescents between the ages of 1 and 18 years is not recommended.

Treatment should not exceed 3 months due to the presence of metoclopramide (see sections 4.4 and 4.8)

### 4.3 Contraindications
- Hypersensitivity to metoclopramide, salicylates or any of the components.
- Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting). In these patients, aspirin has the potential to induce anaphylaxis either on its own or in combination with food and/or exercise.
- Active, chronic or recurrent gastric or duodenal ulcers.
- Congenital or acquired bleeding disorders; obstruction, haemorrhage or perforation of the GI tract.
- Known or suspected phaeochromocytoma.
- Third trimester of pregnancy.
- Metoclopramide should 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.
- Patients with severe hepatic insufficiency
- Patients with severe renal insufficiency (CrCL <30 ml/min).
- 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

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

As salicylates may induce asthma attacks in susceptible individuals MigraMax should be avoided in patients at risk of developing sensitivity reactions. These include individuals with asthma or rhinitis, a history of atopy or nasal polyps, and also patients who have been sensitive to other salicylates or NSAIDs.
Use with caution in patients with a history of gastroduodenal ulcer or GI haemorrhage, or with mild to moderate hepatic impairment, gout, menorrhagia, or epilepsy. Care should be taken in patients using intra-uterine contraceptive devices and patients who have a high alcohol intake.

There is a possible association between aspirin and Reye’s syndrome when given to children with a fever. Reye’s syndrome is a very rare disease which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children under 12 years and should be avoided up to and including 16 years of age if feverish. MigraMax is contraindicated in patients under 18 years of age (see section 4.3).

As total clearance of metoclopramide is reduced and elimination prolonged in patients with renal failure use in patients with significant degrees of renal impairment should be approached with caution.

Metoclopramide may induce an acute hypertensive response in patients with phaeochromocytoma.

Due to the risk of tardive dyskinesia with metoclopramide, treatment should not exceed 3 months (see also sections 4.2 and 4.8).

Extrapyramidal disorders, (drowsiness, decreased level of consciousness, confusion and hallucination) (see section 4.8) 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 may be necessary (benzodiazepines in children and/or anti-cholinergic anti-parksonian drugs in adults).

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.

Methaemoglobinemia has been reported with metoclopramide. In case of methaemoglobinemia, MigraMax should be immediately and permanently discontinued and appropriate measures initiated.

Metoclopramide is not recommended in epileptic patients as benzamides may decrease the epileptic threshold.

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

For acetylsalicylic acid > 500mg/day:
There is some evidence that drugs which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

This drug must be administered under close medical supervision in patients with glucose-6 phosphate dehydrogenase deficiency due to risk of haemolysis (see Section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Metoclopramide-related interactions
Alcohol:
Alcohol potentiates the sedative effect of metoclopramide

Anticholinergics and morphine derivatives:
Anticholinergics and morphine derivatives antagonise the effects of metoclopramide on 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 decreased 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 reported to be reduced by 20% when metoclopramide was administered concomitantly. To avoid toxicity, careful monitoring of ciclosporin plasma concentration is required.

Levodopa:
Levodopa and metoclopramide have a mutual antagonism. Concomitant use should be avoided.

Salicylate-related interactions

Anti-coagulants:
Salicylates may enhance the effects of anti-coagulants.

Oral anti-diabetic agents:
Salicylates may enhance the effects of oral anti-diabetic agents.

Anti-epileptics:
Salicylates may enhance the effects of phenytoin, sodium valproate.

Antimetabolites:
Salicylates may enhance the effects of methotrexate

Immunomodulating agents:
Salicylates may inhibit the action of alpha interferon

Salicylates may interact with other NSAIDs, antacids and glucorticosteroids, which may lower blood salicylate concentration during treatment and result in high levels when treatment is stopped.

The effects of diuretics and uricosurics may also be affected by salicylates.

Other anti-platelet drugs
Salicylates may increase risk of bleeding with clopidogrel and ticlopidine.

Leukotriene antagonists
Aspirin may increase plasma concentration of zafirlukast

Mifepristone
Based on theoretical grounds, mifepristone may interact with salicylates.

### 4.6 Pregnancy and lactation

Although teratogenic effects of acetylsalicylic acid have been recorded in animals, no such effects have been observed in humans. No teratogenic effects have been observed with metoclopramide: data on pregnant patients (> 1000) indicate no malformative nor foeto/ neonatal toxicity during 1rst trimester of pregnancy. A limited amount of data on pregnant patients (> 300) indicate no neonatal toxicity in other trimesters. Animal studies do not indicate reproductive toxicity.

In the third trimester, the use of prostaglandin synthesis inhibitors such as acetylsalicylic acid may expose the foetus to premature closure of the ductus arteriosus. MigraMax is therefore contra-indicated during the third trimester. Like all drugs avoid use in the first and second trimester unless the physician believes the benefits outweigh the risk.

MigraMax is not recommended during lactation because acetylsalicylic acid and metoclopramide 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 Migramax treatment.

4.7 Effects on ability to drive and use machines

MigraMax may cause drowsiness. This effect can be potentiated by CNS depressants or alcohol. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Nervous system and psychiatric disorders
The following reactions, sometimes associated, occur more frequently when high doses are used:
- Extrapyramidal symptoms: acute dystonia and dyskinesia, Parkinsonian syndrome, akathisia may occur even following administration of a single dose of the drug particularly in children, young adults and the elderly (see section 4.4). Extrapyramidal 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 during or after prolonged treatment (see also sections 4.2 and 4.4).
- Metoclopramide may cause lethargy, insomnia, dizziness
- Depression
- Restlessness, anxiety
- Seizures
- Neuroleptic malignant syndrome
- Intracranial haemorrhage

Not known: Intracranial haemorrhage may be fatal, especially in the elderly.

Endocrine disorders
Hyperprolactinaemia causing amenorrhea, galactorrhea, gynaecomastia.

Blood and Lymphatic system disorders
Metoclopramide may cause:
- 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 sulfur-releasing drugs.

Aspirin may increase bleeding time, decrease platelet adhesiveness, and in large doses cause hypothrombinaemia. It may cause other blood disorders, including thrombocytopenia, iron deficiency or haemolytic anaemia and rarely agranulocytosis.

Not known: Thrombocytopenia
Haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency (see section 4.4).

**Cardiac and Vascular disorders**
Bradycardia and heart block have been reported with metoclopramide, particularly the intravenous formulation.

Frequency not known:  
- Transient increase in blood pressure

**Respiratory, thoracic and mediastinal disorders**
Frequency not known:  
- Non-cardiogenic pulmonary oedema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid

**Gastrointestinal disorders**
Diarrrhoea, flatulence
The most common side effects occurring with therapeutic doses of salicylates are gastrointestinal disturbances such as gastric irritation with blood loss, nausea, dyspepsia, vomiting and gastric ulceration. The gastrointestinal haemorrhaging is occasionally severe but in most cases blood loss is not significant.

Frequency not known:  
- Upper gastrointestinal disorders: oesophagitis, erosive duodenitis, erosive gastritis, esophageal ulceration, perforation 
- Lower gastrointestinal disorders: small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, colitis and intestinal perforation
These reactions may or may not be associated with haemorrhage, and may occur at any dose of acetylsalicylic acid and in patients with or without warning symptoms or a previous history of serious GI events

**General disorders and administration site conditions**
Very rarely hypersensitivity, including anaphylaxis has been reported.
Salicylates may induce hypersensitivity especially in those individuals with asthma or rhinitis, and a history of atopy or nasal polyps. The observed hypersensitivity reactions include anaphylaxis, urticara and bronchospasm.

Asthenia

**Ear and labyrinth disorders**
Tinnitus

Renal and urinary disorders
Other reported effects of salicylates include urate kidney stones.

Hepatobiliary disorders
Not known:
- Elevation of hepatic enzymes
- Liver injury mainly hepatocellular
- Chronic hepatitis

Skin and subcutaneous tissue disorders
Not known:
Fixed eruption

4.9 Overdose

In cases of overdose, toxic reactions are mainly ascribable to aspirin. Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (95.1mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms
Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases. A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier. Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Non-cardiogenic pulmonary oedema can occur with acute and chronic acetylsalicylic acid overdose (see section 4.8)

Management
Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic
features. Patients under 10 years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

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

Decreased level of consciousness, confusion and 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacological properties of this product are those of the two active ingredients ie. an analgesic and an antiemetic.

Acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory properties. It inhibits prostaglandin synthesis so that the prostaglandin-induced sensitivity of peripheral nerve endings to kinins and other mediators of pain and inflammation is reduced. Acetylsalicylic acid also exerts a powerful inhibition on platelet aggregation by blocking thromboxane A2 synthesis in the platelets.

Metoclopramide is an effective anti-emetic, although its exact mechanism(s) of action is not fully established. It is a cholinergic agonist acting peripherally to enhance the action of acetylcholine at muscarinic synapses and in the CNS by blocking dopamine receptors in the chemoreceptor trigger zone for vomiting.

Local effects include the promotion of gastric emptying and normal peristalsis, impairment of which are a common feature of migraine attacks.

5.2 Pharmacokinetic properties

Lysine acetylsalicylate

Absorption of lysine acetylsalicylate as a solution is rapid in healthy subjects. Lysine acetylsalicylate dissociates into lysine and acetylsalicylic acid which is rapidly hydrolysed to salicylic acid. The plasma peak of acetylsalicylic acid is achieved within 20 minutes.
Plasma salicylates are essentially bound to plasma proteins and are converted to inactive metabolites in the liver. Salicylic acid and its metabolites are excreted via the kidneys. Clearance increases with increasing urinary pH. The elimination half-life of salicylic acid is dose-dependent owing to the saturable nature of salicylic acid conjugation and ranges from as little as 2 hours after a single dose of 500 mg, lengthening to as long as 20 hours in overdosage.

**Metoclopramide**

The plasma peak of metoclopramide is reached within an average time of 40 minutes following oral administration. Peak plasma concentrations are 32 and 70 g/L for 10 and 20 mg doses. Bioavailability is 80% **per os**. Interindividual variations are related to a 20% first-pass effect. Metoclopramide is rapidly and extensively distributed in tissues. The volume of distribution is 2.2 - 3.4 l/kg. Metoclopramide has a low degree of binding to plasma proteins (30%). The plasma elimination half-life of metoclopramide is 5 - 6 hours. Total clearance is 0.4 - 0.7 l/min.

Metoclopramide is only partially metabolised in humans; urinary excretion occurs essentially as the unchanged and sulfoxoconjugated compounds (50% of the dose administered).

Renal insufficiency significantly reduces the clearance of metoclopramide and increases the plasma elimination half-life.

**Combination**

When administered as an oral solution, lysine acetylsalicylate and metoclopramide are rapidly absorbed.

In subjects not suffering from migraine, plasma concentrations of total salicylates, acetylsalicylic acid and metoclopramide do not differ from those recorded following both drugs administered singly.

The elimination half-life of salicylates and metoclopramide is unaffected in subjects suffering from migraine receiving the two drugs in combination compared with normal subjects.

**5.3 Preclinical safety data**

No data of therapeutic relevance.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame, glycine, lemon flavour (essential oil of lemon absorbed on a maltodextrin substrate).

6.2 Incompatibilities

No known major incompatibilities.

6.3 Shelf life

1 year

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Pack sizes: Carton containing 2 sachets
            Carton containing 6 sachets
            Carton containing 20 sachets

MigraMax is packaged in sachets made of a paper-polyethylene-aluminium complex, containing one unit dose and heat-sealed.

6.6 Special precautions for disposal

Consult the patient leaflet before use.
Do not use after the stated expiry date on the sachet or carton.
To be taken orally when the powder is completely dissolved.
7 MARKETING AUTHORISATION HOLDER

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS, UK

Trading as: Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS, UK
Or
Trading as: Zentiva, One Onslow Street, Guildford, Surrey, GU1 4YS, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 17780/0552

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/03/2011

10 DATE OF REVISION OF THE TEXT

07/11/2016