Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paramax 500mg/5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg paracetamol and metoclopramide hydrochloride equivalent to 5mg metoclopramide.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablets
White, round tablets, engraved "Paramax" on one side with a break-line on the other side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adult population: Paramax is indicated in the management of the symptoms of pain, nausea and vomiting associated with a migraine attack.

4.2 Posology and method of administration

For oral administration only.

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.

It should be noted that total daily dosage of metoclopramide, for young adults (18-20 years), should not normally exceed 0.5mg/kg body weight.

Recommended Dosage:

Adults: Two tablets should be taken at the first warning of a migraine attack. This dosage may be repeated to a maximum of 6 tablets in a 24 hour period.

The maximum daily dose should not exceed 60mg/kg/day of paracetamol (up to a maximum of 4 tablets per day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Elderly patients:
Experience has indicated that normal adult dosage is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

Young adults (18-20 years):
At the first warning of a migraine attack 1 to 2 tablets should be taken. Do not exceed 5 tablets in a 24 hour period.

Children 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.

A presentation of Paramax suitable for the treatment of children under 18 years of age is not available.

Renal impairment:
It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:

Adults:

Glomerular filtration rate	Dose
10-50 ml/min	1 tablet every 6 hours
<10 ml/min	1 tablet every 8 hours

Hepatic impairment:

Severe hepatic impairment: In patients with severe hepatic impairment the dose should be reduced by 50%.

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged.

The daily dose should not exceed 4 tablets per day unless directed by a physician.

4.3 Contraindications

Hypersensitivity to paracetamol, metoclopramide or any of the components.
Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.
Metoclopramide should not be used in the immediate post-operative period (up to 3-4 days) following pyloroplasty or gut anastomosis, as vigorous gastro-intestinal contractions may adversely affect healing.
History of neuroleptic or metoclopramide-induced tardive dyskinesia.
Confirmed epilepsy, as benzamides may decrease the epileptic threshold and increase the frequency and severity of seizures.
Confirmed or suspected phaeochromocytoma, because of the risk of severe hypertension episodes.
Use in children less than 1 year of age due to increased risk of extrapyramidal disorders (see Section 4.4).
Combination with levodopa or dopaminergic agonists because of a mutual antagonism.
Parkinsons disease.
Known history of methemoglobinemia with metoclopramide or of NADH cytochrome-b5 reductase deficiency.

4.4 Special warnings and precautions for use

Paramax should be used with caution and upon medical advice in patients with:

- Hepatic impairment
- Renal impairment (GFR≤50ml/min)
- Chronic alcoholism including recent withdrawal
- Glutathione deficiency
- Glucose 6 phosphate dehydrogenase deficiency
- Gilberts syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Haemolytic anaemia
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

In general, it is advised that treatment with metoclopramide should not exceed 3 months due to the risk of tardive dyskinesia associated with its use.

Drowsiness, decreased level of consciousness, confusion and hallucination occur more frequently when high doses of metoclopramide are used (see section 4.8).

Extrapyramidal disorders 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. Young adults (18-20 years) and the elderly should be treated with care as they are at increased risk of extrapyramidal reactions (see section 4.8). Symptomatic treatment of extrapyramidal reactions may be necessary (anticholinergic anti – Parkinson drugs in adults) (see section 4.9).

Respect the time interval specified in the dosage section between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.

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

Care should be exercised in the event of Paramax being prescribed concurrently with neuroleptics since extra-pyramidal symptoms may occur with both products (see section 4.5).

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

Care is advised in the administration of paracetamol to patients with severe renal or hepatic impairment. The hazards of overdose are greater in those with (non-cirrhotic) alcoholic liver disease. In patients with renal or severe hepatic impairment a dose reduction is recommended (loss of conjugation and increased risk of extrapyramidal effects) – see Section 4.2.

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction (See Section 4.8).

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs). Severe-cutaneous adverse reactions (SCARs): Life threatening cutaneous reactions, Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysys (TEN) have been reported with the use of paracetamol. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop immediately Paramax treatment and seek medical advice.

Metoclopramide may induce Torsade de Pointes, therefore caution should be exercised in patients with known risk factors for prolongation of the QT interval i.e.:
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- Congenital long QT syndrome
- Bradycardia

Concomitant use of medicinal products that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics (see section 4.8)

As with neuroleptics, a Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex characterised by hyperthermia, muscle rigidity, extrapyramidal symptoms, autonomic nervous instability and elevated CPK may occur. Therefore

cautions have to be taken if fever, one of the symptoms of a NMS, occurs and metoclopramide has to be stopped if a NMS is suspected. 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 interactions

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), rifampicin and alcohol.

Paracetamol may increase the risk of bleeding in patients taking warfarin and antivitamin K. Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications.

Co-administration of flucloxacillin with paracetamol may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

Colestyramine can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously.

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

Combination to be avoided:
Levodopa: Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism, concomitant use is therefore contraindicated.
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.

Paracetamol may increase the elimination half-life of chloramphenicol.
Oral contraceptives may increase the rate of paracetamol clearance.
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.
The speed of absorption of paracetamol may be reduced by colestyramine.
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 have both a mutual antagonism with metoclopramide on the digestive tract motility.
CNS depressants (morphine derivatives, hypnotics, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related):
Sedative effects of CNS depressants and metoclopramide are potentiated.
The effects of certain other drugs with potential central stimulant effects eg. monoamine oxidase inhibitors and sympathomimetics may be modified when prescribed with metoclopramide and their dosage may need to be adjusted accordingly.

Neuroleptics:
Metoclopramide may have an additive effect with neuroleptics on the occurrence of extrapyramidal disorders (See warnings).
Due to the prokinetic effect of metoclopramide, the absorption of certain drugs may be modified.

Serotoninergic drugs:
The use of metoclopramide with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) may increase the risk or serotonin syndrome.

Digoxin:
Metoclopramide decreases digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Ciclosporin:
Metoclopramide increases cyclosporin 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 is required.

Mivacurium and suxamethonium:
Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

Strong CYP2D6 inhibitors such as fluoxetine:
Metoclopramide exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine.

4.6 Fertility, pregnancy and lactation

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.

Paracetamol: A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy 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 1st 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. The use of metoclopramide may be considered during pregnancy, if necessary.

Due to the pharmacological properties, as other benzamides, in case of metoclopramide administration before delivery, extrapyramidal disorders in newborn cannot be excluded.

Exposure of pregnant women to the individual active components indicate 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.

During lactation, metoclopramide and paracetamol are excreted in the 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

Drowsiness and dizziness may occur following administration of metoclopramide, resulting in impaired ability to drive vehicles or operate machines, particularly if Paramax is administered with CNS depressants or alcohol (see section 4.5).

4.8 Undesirable effects

Central nervous system and psychiatric disorders

The following reactions, sometimes associated, occur more frequently when high doses are used:

Extrapyramidal symptoms may occur. Acute dystonia (including visual disturbances and oculogyric crises) and dyskinesia, parkinsonian syndrome, akathisia may increase, even following administration of a single dose, particularly in young adults (see section 4.4). The incidence of extrapyramidal symptoms in young adults may increase if the metoclopramide dosage exceeds 0.5mg/kg body weight/day.

Although rare, tardive dyskineisa may be irreversible.

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, restlessness, anxiety, confusion, suicidal ideation.

Other reactions may occur:
- Tardive dyskinesia can occur during use or after prolonged use, particularly in elderly patients (see section 4.4).
- Restlessness, anxiety and dizziness.
- Depression.
- Seizures
- Neuroleptic malignant syndrome.

Gastro-intestinal disorders
Diarrhoea

Haematological disorders
Very rare (less than 0.01%) cases of methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency have been reported, particularly in neonates. (see section 4.4).
Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing drugs.
Blood dyscrasias including thrombocytopenia and agranulocytosis.
Haemolytic anaemia, in particular in patients with underlying glucose 6-phosphate-deshydrogenase deficiency.

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

Body as a whole
Very rarely hypersensitivity, including anaphylaxis has been reported.
Asthenia.
Skin rash.

Cardiovascular disorders
Hypotension especially with intravenous formulation.
Blood pressure increase in patients with or without phaeochromocytoma (see section 4.3).
QT prolongation and torsade de pointes (see section 4.4).
Very rarely (less than 0.01%) cases of bradycardia and atrioventricular block have been reported with metoclopramide, particularly with the intravenous formulation.
Not known: Transient increase in blood pressure.

Respiratory, thoracic and mediastinal disorders

Not known: bronchospasm (see section 4.5).

Immune system disorders

Anaphylactic shock, angioedema.

Skin and subcutaneous disorders
Very rare cases of serious skin reactions such as Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, and fixed drug eruption (see section 4.4) have been reported.

Hepatobiliary disorders
cytolytic hepatitis, which may lead to acute hepatic failure

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Paracetamol overdose

There is a risk of poisoning with paracetamol particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, disseminated intravascular coagulation and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors include: If the patient;
- Is on long-term treatment with carbamazepine, phenobarbitone, 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 depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Emergency Procedure:
Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if>150mg/kg paracetamol has been taken within 1 hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with National treatment guidelines.

Symptomatic treatment should be implemented.

Metoclopramide overdose

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 symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian drugs in adults).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The mechanism of action of metoclopramide in the gastrointestinal tract remains unclear. It is thought 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.

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.

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 500mg/5mg tablets (1g paracetamol + 10mg metoclopramide), Panadol tablets (1g paracetamol) and Solpadeine effervescent tablets (1g paracetamol + 16mg codeine phosphate+16g caffeine), absorption of paracetamol from Paramax 500mg/5mg tablets was found not to differ significantly from absorption from Panadol or Solpadeine.

Oral paracetamol is largely absorbed from the small intestine, the rate of absorption depending on the rate of gastric emptying.

Gastric emptying is often severely delayed during migraine attacks; absorption of oral paracetamol has been shown to be delayed and impaired during a migraine attack compared to when the same patients are headache free.

Metoclopramide stimulates gastric emptying and has been shown to accelerate absorption of paracetamol.

5.3 Preclinical safety data

Paracetamol and metoclopramide hydrochloride are well established drug substances and results of preclinical testing are well documented.

Paracetamol
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Colloidal anhydrous silica
Magnesium stearate
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect the product from light.

6.5 Nature and contents of container

PVC/aluminium blister packs or PVC (250 micrometre) aluminium foil (20 micrometre)/PVC (15 micrometre) blister packs of 14, 30, 42, 100 and 108 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special instructions for use.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/154/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 September 1995
Date of last renewal: 31 October 2009

10 DATE OF REVISION OF THE TEXT

December 2019