SPASMALGIN TABLETS

1. NAME OF THE MEDICINAL PRODUCT

SPASMALGIN tablets

Active pharmaceutical ingredient:
Paracetamol 150mg
Papaverine HCL 80mg
Codeine Phosphate 10 mg
Atropine Sulphate 0.4mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Paracetamol 150mg
Papaverine HCL 80mg
Codeine Phosphate 10 mg
Atropine Sulphate 0.4mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Tablets.
Tablets packaged in a tray.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Analgesic and antispasmodic for the digestive system, the kidneys and the gall bladder.

This medicine is not intended for children under the age of 12 years.

Medicines containing codeine should only be used to treat sharp pain (of short duration) of moderate intensity among children and adolescents above the age

of 12 years, and only if the pain cannot be treated by pain relievers such as paracetamol or ibuprofen, since use of codeine may increase the risk of respiratory depression.

4.2 Posology and method of administration

Adults

The recommended daily dose: …….

Do not exceed a dosage of 8 tablets in 24 hours.

In case there is no improvement within 3 days, the situation should be re-evaluated.

Children and adolescents
This medicine is not intended for children under the age of 12 years.

Paracetamol & Codeine:
Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine.

Elderly:
The normal dose is considered appropriate in elderly patients.
Not to be taken for more than 3 days continuously without medical assessment.

Method and administration:

The medicine should be taken with or after a meal, swallowed with water.
The tablets can be crushed before use, not to be stored as crushed tablets.
This medicine is to be taken at specific time intervals. If forgotten, the dose should be taken as soon as remembered but two doses should not be taken at the same time. The next dose can be taken at the regular time.

Attention:
The medicine should be taken at least 2 hours before taking osmotic laxatives and antacids. And 6 hours before injecting digoxin.

4.3 Contraindications

The medicine should not be used in the following cases:
The patient is pregnant or breast feeding,
Sensitivity (allergy) to the active ingredients or to any of the other ingredients contained in the medicine. For the full list of excipients, see section 6.1.
Children under the age of 12 years.
Children and adolescents above the age of 12 and under the age of 18 after a tonsillectomy or adenoidectomy for treatment obstructive sleep apnea, since these patients are more likely than others to suffer from breathing problems and there is an increased risk of developing serious and life-threatening adverse reactions.
In case the patient knows he produces a significant amount of morphine from a dose of codeine (belonging to the ultra-rapid metabolisers group), as he is at increased risk of suffering from severe side effects when using codeine.

Paracetamol & Codeine:
In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

Atropine:

Atropine is contraindicated in patients with:

prostatic enlargement, as it may lead to urinary retention.

paralytic ileus or pyloric stenosis.

angle-closure glaucoma or in patients with a narrow angle between the iris and the cornea as it may raise intra-ocular pressure and precipitate an acute attack.

myasthenia gravis (except to reduce muscarinic side effects of anticholinesterases).

Papaverine:
Papaverine is contraindicated in:
Complete atrioventricular heart block.
Administer with extreme caution when cardiac conduction is depressed, because of increased risk of transient ectopic rhythms of ventricular origin (premature beats or paroxysmal tachycardia).

4.4 Special warnings and precautions for use

Sensitivity to any food or medicine.

Naturally and rarely, in some people's bodies, codeine undergoes metabolism (breakdown) more rapidly than in most of the population. In these rare cases, high amounts of metabolites may accumulate and can cause severe side effects, such as: excessive drowsiness, confusing our shallow breathing. In such cases, the patient should be referred immediately for medical treatment.

In most cases, it is impossible to know in advance whether a patient belongs to this group of people at risk for this effect.

Current or past impaired function of: the respiratory system (e.g., asthma), the heart and/or blood vessels, the liver, the kidney/urinary tract, the digestive system (in retinal diseases, diarrhoea, reflux esophagitis, the thyroid, the roostate, from spasms, from severe muscle weakness.

Paracetamol may cause liver damage in the following cases: if given for a prolonged period, drinking alcoholic beverages during the treatment period and if other medicines that effect the liver are used.

Paracetamol may interfere with blood sugar test results.

Prolonged use may cause dependence!

Not to be used frequently or for prolonged period without consultation.

Other fever- and pain -reducing medicines, or cold medicines, should not be taken- to prevent paracetamol poisoning/overdose.

Medicines containing codeine are only used to treat sharp pain (of short duration) of moderate intensity among children above the age of 12 years, and only if the pain cannot be treated by pain relievers such as paracetamol or ibuprofen, since use of codeine may increase the risk of breathing suppressing.

Do not give codeine to children and adolescents above the age of 12 and under the age of 18 after a tonsillectomy or adenoidectomy for treatment of obstructive sleep apnoea, since these patients are more likely than others to suffer from breathing problems.

This medicine is not recommended for children suffering from breathing problems.

Atropine may distrust the results of a gastric acid secretion test- do not take this medicine for 24 hours before the test.

Paracetamol & Codeine:

Codeine is metablised by the liver enzyme CYP2D6 into morphine, its active metabolite.

If a patient has a deficiency or is completely lacking this enzyme, an adequate analgesic effect will not be obtained.

If the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses.

These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite.

In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal.

Post operative use in children:

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events including death.

All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function:

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5- oxoproline, is recommended.

Atropine:

Use with caution in patients with:

urinary retention, acute myocardial infarction, hypertension, conditions associated with tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia and diarrhoea.

Use of atropine in patients with ulcerative colitis may lead to toxic megacolon and ileus.

Increased side effects may be seen in children and the elderly, and in patients with Down's syndrome.

Atropine may aggravate gastro-oesophageal reflux.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Papaverine:

Sensitivity Reactions

Hepatic Hypersensitivity

Hepatic hypersensitivity with GI symptoms, jaundice, eosinophilia, and altered hepatic function tests results reported.

If such hypersensitivity occurs, the drug should be discontinued.

Glaucoma

Use with caution in patients with glaucoma.

Abuse and Dependence

Potential abuse and dependence to papaverine reported.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin or salicylates
Medicines that influence the central nervus system (e.g., phenothiazines, sedatives, hypnotics, medicines for Parkinson, for spasms, antihistamines for allergies, anesthetics for surgery and narcotics pain relivers).
Anticoagulants
Anti-depressants from MAOI type
Other non-steroidal anti-inflammatory preparations or other pain or fever reducing medicines
Antichoolinergics (e.g., abdominal antispasmodics)
Medicines that include liver enzyme activity, such as barbiturates or phenytoin (for spasms)
Antispasmodics
Potassium chloride

Paracetamol & Codeine:

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

The anticoagulation 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.

Alcohol and drugs which induce hepatic microsomal enzymes e.g. antiepileptic drugs, may increase the hepatotoxicity of paracetamol, particularly after overdose.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

The depressant effects of codeine are enhanced by depressants of the central nervous system such as hypnotics, sedatives tricyclic antidepressants and phenothiazines.

Codeine may antagonise the gastrointestinal effects of metoclopramide and domperidone. Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors.

Atropine:

Alcohol: Marked impairment of attention can occur with alcohol, sufficient to make driving more hazardous.

Anti-arrhythmics: Increased antimuscarinic side-effects may occur with disopyramide.

The absorption of mexiletine can be delayed by atropine but the extent of absorption is unaltered and no special precautions are necessary.

Anticholinergics: Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation; concomitant use can lead to confusion in the elderly.

Antidepressants: Increased antimuscarinic side-effects may occur with tricyclic antidepressants and mono-amine oxidase inhibitors (MAOIs).

Antifungals: The absorption of ketoconazole can be reduced by atropine.

Antihistamines: Increased antimuscarinic side-effects may occur with some antihistamines.

Antipsychotics: Increased antimuscarinic side-effects may occur with phenothiazines and clozapine.

Antivirals and Dopaminergics: Increased antimuscarinic side-effects may occur with amantadine.

The absorption of levodopa may possibly be reduced when administered with antimuscarinic agents.

Metoclopramide and domperidone: Possible antagonism of gastrointestinal effects.

Nitrates: The common side-effect of a dry mouth with atropine may result in the failure of sublingual nitrates to dissolve, thereby reducing their effectiveness.

Parasympathomimetics: Possible antagonism of effect of parasympathomimetics. Phenylephrine.

Papaverine:

- Cipro (ciprofloxacin)- major
- Viagra (sildenafil)-moderate
- L-Arginine (arginine)- moderate
- Cialis (tadalafil)-minor

Unknown:

- Acetylsalicylic Acid (aspirin)
- Adrenalin (epinephrine)
- Alcohol (contained in alcoholic beverages) (ethanol)
- Aspirin Low Strength (aspirin)
- Benadryl (diphenhydramine)
- Celebrex (celecoxib)
- CoQ10 (ubiquinone)
- Crestor (rosuvastatin)
- Eliquis (apixaban)
- Fish Oil (omega-3 polyunsaturated fatty acids)
- Flonase (fluticasone nasal)
- Ginkgo Biloba (ginkgo)
- Metoprolol Succinate ER (metoprolol)
- Metoprolol Tartrate (metoprolol)
- MiraLAX (polyethylene glycol 3350)
- Neurontin (gabapentin)
- Paracetamol (acetaminophen)
- Prilosec (omeprazole)
- Tylenol (acetaminophen)
- Vitamin B1 (thiamine)

- Vitamin B12 (cyanocobalamin)
- Vitamin B6 (pyridoxine)
- Vitamin C (ascorbic acid)
- Vitamin D3 (cholecalciferol)
- Vitamin K1 (phytonadione)
- Xarelto (rivaroxaban)

Papaverine disease interactions:

- complete AV heart block
- glaucoma

4.6 Fertility, pregnancy and lactation

The medicine is forbidden to use during pregnancy and breastfeeding

Paracetamol & Codeine:

The safety of paracetamol and codeine tablets during pregnancy has not been established and in view of the possible association of codeine with respiratory depression and heart malformations, use during this period should be avoided.

Codeine should not be used during breastfeeding.

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses.

If the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

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.

Atropine:

Atropine crosses the placenta and traces are found in breast milk. It should therefore only be used with caution.

Papaverine:

Pregnancy

Risk cannot be ruled out. There are no satisfactory studies in pregnant women, but animal studies demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks

Lactation

Not known whether papaverine distributes into human milk. Use with caution in nursing women.

4.7 Effects on ability to drive and use machines

Do not drive or operate dangerous machines while using the medicine since use of this medicine may impair alertness.

Children should be cautioned against bicycle riding or laying near road, etc.

4.8 Undesirable effects

As with any medicine, use of this medicine may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

The medicine should be stooped as soon as possible in case of dizziness, blurred vision, accelerated heart rate, appearance of jaundice, abnormal liver activity, hypersensitivity (rash or skin irritation, shortness of breath or difficulty breathing), increased drowsiness, eye pain.

In the elderly-

Confusion and restlessness, difficulty in passing urine, eosinophilia (rare).

Additional side effects:

Dry mouth, constipation, nausea/vomiting, drowsiness, headache, digestive system disturbances, increased seating.

Paracetamol & Codeine:

The most common side effects are:

nausea, vomiting, constipation, dry mouth, sweating, skin rashes and other allergic reactions.

There have been reports of:

blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Paracetamol: very rare cases of serious skin reactions have been reported.

Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a painkiller for headaches can make them worse.

Atropine:

Some of the central effects of atropine seen at toxic doses may also occur at therapeutic doses.

Immune system disorders, Hypersensitivity.

In rare cases a fever may develop.

Psychiatric disorders, Confusional states (particularly in the elderly).

Nervous system disorders, Occasionally giddiness and staggering may occur.

Eye disorders, Dilation of the pupils with loss of accommodation and photophobia.

Increased intraocular pressure.

In rare cases, angle-closure glaucoma may develop.

Cardiac disorders, Transient bradycardia, followed by tachycardia, palpitations and arrhythmias.

Respiratory, thoracic and mediastinal disorders Bronchial secretions may be reduced, with formation of mucous plugs.

Gastrointestinal disorders, Dry mouth with difficulty in swallowing, thirst.

Occasionally nausea and vomiting may occur.

A reduction in the tone and mobility of the gastro-intestinal tract may lead to constipation.

Increased gastric reflux may result in retrosternal pain.

Skin and subcutaneous tissue disorders Flushing and dryness of the skin. Rashes.

Renal and urinary disorders, Urinary urgency, difficulty or retention.

Papaverine:

Common Adverse Effects

Nausea, abdominal
distress, anorexia, constipation, malaise, drowsiness, vertigo, sweating, headache, diarr hea, rash, flushing of the face, increased heart rate, increased depth of respirations, slight increase in BP, sedation.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

4.9 Overdose

In case of overdose or if a child has accidently swallowed the medicine, immediate visit to a doctor or a hospital emergency room with the package of the medicine is required.

Paracetamol& Codeine:

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 a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes. or b) Regularly consumes ethanol in excess of recommended amounts. or c) Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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 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 overdosage.

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.

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) but results should not delay initiation of treatment beyond 8 hours after ingestion, as 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.

The effects of codeine in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been coingested, including alcohol, or the overdose is very large.

The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable.

Consider activated charcoal if an adult presents within one hour of ingestion of more than 350mg or a child more than 5mg/kg. Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 4 hours after ingestion.

Atropine:

There is considerable variation in susceptibility to atropine; recovery has occurred even after 1g, whereas deaths have been reported from doses of 100mg or less for adults and 10mg for children.

Symptoms of overdose: In overdose, the peripheral effects become more pronounced such as dilation of pupils, continuing blurred vision, or changes in near vision, severe dryness of mouth, nose or throat, dizziness and drowsiness. Other symptoms such as rapid respiration, increased respiratory rate, difficulty in breathing, increased heartbeat, hypertension, hyperthermia, fever, muscle weakness, inhibition of micturition, nausea and vomiting may occur. A rash may appear on the face, neck or upper trunk, and there may be unusual warmth, dryness or flushing of the skin.

Toxic doses also cause CNS stimulation marked by nervousness, restlessness, irritability, confusion, excitement, ataxia, incoordination, slurred speech, paranoid and psychotic reactions, hallucinations and delirium and occasionally seizures. In severe overdose, central stimulation may give way to CNS depression, coma, circulatory and respiratory failure and death.

Treatment of overdose: If a patient presents within an hour of an overdose of atropine by mouth, the stomach may be emptied (but only if a life-threatening amount has been ingested) or activated charcoal given to reduce absorption. Diazepam may be given to control marked excitement and convulsions. Hypoxia and acidosis should be corrected. If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation consider correction with intravenous sodium bicarbonate. Antiarrhythmics are not recommended if arrhythmias develop. Phenothiazines should not be given as

they may exacerbate antimuscarinic effects. Supportive therapy should be given as required.

5. PHARMACOLOGICAL PROPERTIES

Paracetamol & Codeine:

5.1 Pharmacodynamic properties

Paracetamol is a peripherally acting analgesic with antipyretic activity.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine.

Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

Atropine:

Atropine is an antimuscarinic agent. These substances are competitive inhibitors of acetylcholine at muscarinic receptors of autonomic effector sites with parasympathetic innervation.

5.2 Pharmacokinetic properties

Paracetamol & Codeine:

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol.

The elimination half life varies from about 1-4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose dependent.

Codeine phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour.

Codeine is metabolised by O- and N-Demethylation in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

The plasma half life has been reported to be between 3 and 4 hours.

Atropine:

Atropine is readily absorbed from the gastro-intestinal tract and mucous membranes.

It is rapidly cleared from the blood and is distributed through the body, crossing the blood-brain barrier. It is completely metabolised in the liver and is excreted in the urine as unchanged drug and metabolites.

5.3 Preclinical Safety Data

Paracetamol & Codeine:

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

Atropine:

There are no preclinical data of relevance to the prescriber which are additional to those already included in other sections.

Papaverine:

Absorption- Readily absorbed from GI tract.

Distribution- Distributed throughout the body, with highest concentrations in fat deposits and liver.

Not known if papaverine distributes into human milk.

Plasma Protein Binding- 90%.

Elimination- Rapidly metabolized in the liver.

Elimination Route- Excreted in urine, principally as inactive metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In addition of the active ingredients, the medicine also contains:
Powdered Cellulose, Microcrystalline Cellulose, Lactose, Magnesium Stearate, Colloidal Silicon Dioxide, Sodium Starch Glycolate.

Each tablet contains 6mg of lactose and less than 1 mg of sodium.

6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage

Store at temperature below 25 °C.
Keep medicine out of the reach of children.
Store in the original pack and to protect the substance from light.

6.5 Nature and contents of container

Tablets are packaged in trays, 30 tablets in a package.

6.6 Special precautions for disposal and other handling

7. MARKETING AUTHORISATION HOLDER

Sam-On Ltd.
25 Ehud Kinnamon (haavoda) St.
Bat-Yam 59602

8. MARKETING AUTHORISATION NUMBER

363622208

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10. DATE OF REVISION OF THE TEXT

11. PRESCRIPTION STATE

By prescription only

Ref:

https://mhraproducts4853.blob.core.windows.net/docs/ae586b5078bcf3e9086bf06a43fe2a5e581e535e

https://mhraproducts4853.blob.core.windows.net/docs/5f1d4016487f0ba80c325efcd14404330da44589

https://www.drugs.com/monograph/papaverine.html