SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SPAZMOL PLUS 10 mg/500 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance(s):
Hyoscine-N-butylbromide 10.0 mg
Paracetamol 500.0 mg
Excipient(s) with known effect:
Croscarmellose sodium 40.0 mg
Tartrazine
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
Yellow, round, slightly curved, odorless, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for paroxysmal pain in diseases of the stomach and intestines, dysfunction of the biliary and urinary ducts and female genital organs (e.g. dysmenorrhea), and spastic pain.

4.2 Posology and method of administration

Posology:
Unless another use is recommended by the doctor,
In adults: 1-2 tablets 3 times a day.

Frequency and duration of administration:
The total daily dose should not exceed 6 tablets.
SPAZMOL PLUS should not be used for a long time or in high doses without the approval of a physician.

Method of administration:
For oral use. The film-coated tablets should be swallowed whole, with a glass of water.

Additional information on special populations:
Renal / Hepatic impairment:
Caution and physician's supervision is advised in patients with renal and hepatic impairment.

Pediatric population:
These film-coated tablets are not suitable for use in children under 10 years of age.

Geriatric population:
No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

4.3 Contraindications

- Patients with hypersensitivity to hyoscine-N-butylbromide, paracetamol or any other component of the product
- Untreated narrow-angle glaucoma
- Prostatic hypertrophy with urinary retention
- Mechanical stenosis of the gastrointestinal tract or paralytic ileus
- Tachycardia
- Megacolon
- Myasthenia gravis

4.4 Special warnings and precautions for use

It should be used with caution in patients with Gilbert's Syndrome (Meulengracht).

Caution and physician's supervision is advised in patients with anemia, lung disease, and renal or hepatic impairment.

Acute, high-doses lead to severe liver toxicity. Chronic daily doses in adults may cause liver damage. Caution must be exercised in patients with alcoholic liver disease.

Caution must be exercised in patients with narrow angle glaucoma, intestinal or urinary outlet obstruction as well as in patients at risk of developing tachyarrhythmia such as thyrotoxicosis, cardiac insufficiency and cardiac surgery. SPAZMOL PLUS should only be used under medical supervision and the dose should be reduced or administered less frequently if necessary in such cases.

In first-time users of paracetamol or those with a history of previous use, redness of the skin, rash or a skin reaction may occur during the first dose or repeated doses. In this case, it is necessary to contact the doctor, stop taking the medication and switch to an alternative treatment. People who have had a skin reaction to paracetamol should not use this medicine or any other medicine containing paracetamol again. This can cause skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP), which can be severe and fatal.

Caution must be exercised in thyroid gland disorders leading to hyperthyroidism, constipation and hyperthermia cases.

This medicinal product contains less than 1 mmol (23 mg) of sodium in each dose; no sodium-related side effects are expected at this dose.

This product contains tartrazine. It may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

SPAZMOL PLUS enhances the anticholinergic effects of tricyclic antidepressants, antihistamines, quinidine, amantadine, butyrophenones, phenothiazines, dizopramide and other anticholinergic medicines (e.g. tiotropium, ipratropium).

Accelerated gastric emptying after administration of medicines such as metoclopramide results in an increased rate of absorption. Concomitant treatment with dopamine antagonists such as metoclopramide may result in diminution of the effects of both medicinal products on the

gastrointestinal tract.

SPAZMOL PLUS increases the tachycardic effects of beta-adrenergic medicines.

Normally safe doses of paracetamol may cause liver damage when taken concomitantly with certain hypnotics and anti-epileptics (e.g. glutethimide, phenobarbital, phenytoin, carbamazepine) or enzyme-inducing medicines such as rifampicin. This also applies to alcohol consumption.

In cases where gastric emptying is slowed down with medicines such as propantheline, the onset of the effect is delayed as a result of the reduced absorption rate of paracetamol.

When combined with chloramphenicol, the risk of toxicity is increased as the half-life of chloramphenicol may increase.

The clinical implications of interactions between paracetamol and warfarin have not yet been evaluated, as with coumarin derivatives. Therefore, if paracetamol is to be given for a prolonged period to patients on oral anticoagulant therapy, the patient should be closely monitored.

Concomitant use of paracetamol and AZT (zidovudine) may lead to a decrease in leukocyte counts. Therefore, SPAZMOL PLUS and AZT should not be used concomitantly without the advice of a doctor.

Additional information on special populations:
No specific data available.

Pediatric population:
No specific data available.

4.6 Pregnancy and lactation
General advice
Pregnancy category is C.

Women with childbearing potential / Contraception
There are insufficient data on the use of SPAZMOL PLUS tablets in women of childbearing potential.

Pregnancy
Long-term experiences have shown no evidence of harmful effects during pregnancy. SPAZMOL PLUS should not be used during pregnancy, especially in the first trimester, unless necessary. General warnings regarding the use of medicines during pregnancy, especially in the first trimester, should be observed.

Lactation
Safety of hyoscine-N-butylbromide in breast-feeding women has not yet been established.

Paracetamol is excreted in breast milk, but no effect on the infant is predicted when used in therapeutic doses.

The safety of SPAZMOL PLUS during lactation has not been established. Breastfeeding should be stopped during treatment with SPAZMOL PLUS.

Fertility
Studies conducted in animals are insufficient in terms of effects on pregnancy /and-or/ embryonic/fetal development /and-or/ parturition /and-or/ postnatal development (see section 5.3.). The potential risk to humans is unknown.

4.7 Effects on ability to drive and use machines
There is no data for effects on driving and using machines. Some patients may have impaired adaptation to near and far vision. Patients with signs of visual impairment should not drive or operate machinery.

4.8 Undesirable effects
Frequencies of undesirable events listed below by the system organ class are defined as follows: Very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1,000, < 1/100); rare (≥1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated based on available data).

Blood and lymphatic system disorders
Not known: Pancytopenia, agranulocytosis, thrombocytopenia, leukopenia

Immune system disorders, skin and subcutaneous tissue disorders
Uncommon: Dyshidrosis, skin reactions, nausea
Rare: Decreased blood pressure, skin rash, pruritus, urticaria, allergic edema and angioedema, acute generalized exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (including fatal outcomes)
Not known: Anaphylactic shock, anaphylactic reactions, hypersensitivity, shock

Cardiac disorders
Rare: Tachycardia

Respiratory, thoracic and mediastinal disorders
Unknown: Bronchospasm (particularly in patients with a history of bronchial asthma or allergy)

Gastrointestinal disorders
Uncommon: Dry mouth

Hepatobiliary disorders
Unknown: Increased transaminases

Renal and urinary disorders
Unknown: Urinary retention

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting

system.

4.9 Overdose

Hyoscine-N-butylbromide

There are no data available on the symptoms of intoxication due to acute dosing with hyoscine-N-butylbromide in humans. In case of overdose, anticholinergic symptoms such as urinary retention, dry mouth, skin rash, decreased gastrointestinal motility, transient visual disturbances, orthostatic hypotension and Cheyne-Stokes respiration may occur.

Paracetamol

In adults who have taken more than 10 g there is a possibility of toxicity. Moreover, the harm of overdose is greater in those with alcoholic liver disease without cirrhosis. Liver damage following overdose in children is relatively rare. Paracetamol half-life of about 2 hours in normal adults is generally prolonged to 4 hours or more in paracetamol overdose along with the liver cell damage. A decrease in $^{14}CO_2$ excretion has been reported after ^{14}C-aminopyrine. This better correlates paracetamol overdose with liver cell damage than plasma paracetamol concentration or half-life, or conventional liver function test measurements. Renal failure may occur due to acute tubular necrosis following paracetamol-induced fulminant hepatic failure. However, incidence in this group of patients is not higher compared to those observed in patients with fulminant hepatic impairment due to other reasons. Rarely, renal tubular necrosis may occur with only minimal hepatic toxicity 2-10 days after taking the medicine. Chronic alcohol intake was reported to contribute to the development of acute pancreatitis in a patient who had overdosed on paracetamol. In addition to acute overdose, liver damage and nephrotoxic effects have been reported after excessive daily intake of paracetamol.

Symptoms

Pallor, anorexia, nausea and vomiting are common early symptoms of paracetamol overdose. Hepatic necrosis is a dose-related complication of paracetamol overdose. Hepatic enzymes may increase and prothrombine time may prolong within 12 to 48 hours, but clinical symptoms may not be evident within 1 to 6 days following the intake of medicine.

Treatment

Paracetamol overdosage should be treated immediately to protect the patient against delayed hepatotoxicity. This requires reducing absorption (gastric lavage or active charcoal) followed by intravenous N-acetylcysteine or oral methionine. Methionine should not be used if the patient is vomiting or conjugated with activated charcoal. Peak plasma paracetamol concentrations may be delayed up to 4 hours following an overdose. Therefore, plasma paracetamol levels should be measured at least 4 hours after medicine ingestion to determine the risk of hepatotoxicity. Additional treatment (additional oral methionine or intravenous N-acetylcysteine) should be considered in the light of blood paracetamol content and time elapsed since medicine intake. It is recommended to lower the threshold for treatment with N-acetylcysteine by 30-50% in patients taking hepatic enzyme-inducing medicines, those with long-standing alcohol addiction or those who are chronically malnourished, as these patients may be more sensitive to the toxic effects of paracetamol. Treatment of fulminant hepatic failure following paracetamol overdosage may require specialization.

In case of overdose, parasympathomimetic drugs may be administered if necessary for anticholinergic effects that may occur due to hyoscine butylbromide. In cases of glaucoma, an ophthalmologist should be consulted urgently. Cardiovascular complications should be treated

according to usual therapeutic principles. Intubation and artificial respiration should be considered in case of respiratory failure. Catheterization may be required for urinary retention. In addition, appropriate supportive measures should be taken where necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antispasmodics in combination with analgesics
ATC code: A03DB04

Hyoscine-N-butylbromide:
Hyoscine-N-butylbromide, a spasmolytic agent contained in SPAZMOL PLUS, is a semi-synthetic derivative of scopolamine found in plants. Hyoscine-N-butylbromide with four ammonium components has a peripheral anticholinergic effect. This effect is due to the parasympatholytic effect on the inhibition of ganglion transmission.

Hyoscine-N-butylbromide has a spasmolytic effect on the smooth muscles of the gastro-intestinal, biliary and urinary tract ducts. A similar effect on uterine muscles was observed *in vitro in* human uterine tissue samples. The analgesic properties of paracetamol enhance this effect. Due to its combined antispasmodic and analgesic properties, SPAZMOL PLUS is a suitable preparation for the treatment of paroxysmal pain of the luminal organs, especially in the abdomen.

5.2 Pharmacokinetic properties

Hyoscine-N-butylbromide:
Absorption:
As a quaternary ammonium compound, hyoscine-N-butylbromide is highly polar and hence only partially absorbed following oral (8%) and rectal (3%) administration. Systemic bioavailability has been found to be less than 1%.

Distribution:
Although measurable blood levels are very low, hyoscine-N-butylbromide and its metabolites are found in very high concentrations at sites of action such as the gastrointestinal tract, gallbladder, bile ducts, liver and kidneys.

Hyoscine-N-butylbromide does not cross the blood-brain barrier and has low binding to plasma proteins.

Biotransformation:
The half-life of the terminal elimination period ($t_{1/2}$gamma) is approximately 5 hours.

Elimination:
Following intravenous administration, total clearance is 1.2 l/min and approximately half of the clearance occurs through the kidneys. The main metabolites excreted in the urine bind poorly to the muscarinic receptors.

Paracetamol:
Absorption:
After oral administration, almost all of paracetamol is rapidly absorbed from the small intestine and reaches peak plasma concentrations in approximately 0.5 to 2 hours. Absolute

bioavailability rates between 65% and 89% indicate a first-pass effect.

Distribution:
The medicine is rapidly and evenly distributed into tissues. Binding to plasma proteins is low at therapeutic doses.

Biotransformation:
In the liver, paracetamol is converted into inactive compounds of glucuronic (about 60%) and sulfuric acid (about 35%).

The plasma half-life at therapeutic doses is between 1.5-3 hours. In children, the half-life is prolonged and it is metabolized by sulfate conjugation. In chronic liver disease, the plasma half-life of paracetamol is also prolonged.

Elimination:
All inactive glucuronic and sulfuric acid compounds are excreted in the urine within 24 hours. Less than 5% of the dose taken is excreted unchanged.

Linearity/non-linearity:
Not applicable.

Characteristics in patients
Pediatric:
Paracetamol: In children, the half-life is prolonged and it is metabolized by sulfate conjugation.

Renal / Hepatic impairment:
Paracetamol: In chronic liver disease, the plasma half-life of paracetamol is also prolonged.

5.3 Preclinical safety data
Animal studies showed no evidence of teratogenicity, carcinogenicity or negative effect on fertility.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Polyvinylpyrrolidone K25
Microcrystalline cellulose
Croscarmellose sodium
Silicon dioxide
Magnesium stearate
Film coating agents (Opadry 03-B-22320 Yellow):
- Hydroxypropylmethylcellulose (E 464)
- Titanium dioxide (E 171)
- Polyethylene glycol
- Tartrazine (E 102)
- Indigo carmine (E 132)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at room temperature below 25°C.

6.5 Nature and contents of container
Blisters containing 10 film-coated tablets covered with transparent PVC on one side and printed aluminum foil on the other side. Each cardboard box includes 20 film-coated tablets.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
DEVA HOLDİNG A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)
179/49

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Date of first authorization : 24.09.1996
Renewal of the authorization : 26.03.2013

10. DATE OF REVISION OF THE TEXT
12.12.2014