

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SPANOL® 40 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMBINATION

Active substance

Otilonium bromide	40 mg
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Excipients:

Lactose monohydrate from bovine origin	53.0 mg
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Sodium starch glycolate	2.0 mg
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See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, round film-coated tablets.

4 CLINICAL FEATURES

4.1 Therapeutic indications

Antispasmodic in irritable bowel syndrome (IBS) and spastic-painful conditions of the distal enteric region.

4.2 Posology and route of administration

Posology/frequency and duration of administration:

Use one tablet 2-3 times a day according to your doctor's recommendation.

Mode of application:

The tablets are swallowed whole with a little water, preferably 20 minutes before meals.

Additional information on special populations:

Renal/liver failure:

SPANOL® is absorbed systemically by 3%, its effect is local and is not affected by renal and hepatic dysfunction. Therefore, no dose adjustment is required for SPANOL® in these patients.

Pediatric population:

There is no clinical data on its use in the pediatric population, therefore the use of SPANOL® in children is not recommended.

Geriatric population:

Use one tablet 2-3 times a day according to your doctor's recommendation.

4.3. Contraindications

- Known hypersensitivity to the active substance or any of the excipients
- It should not be used in case of colon obstruction.

4.4 Special warnings and precautions for use

Patients with glaucoma, prostatic hypertrophy and pyloric stenosis should use this medicine with caution.

Otilonium bromide has a relaxing effect on the smooth muscles of the gastrointestinal tract and should be used with caution in cases characterized by constipation and intestinal atony, especially in diabetic patients.

Patients with rare inherited galactose intolerance, Lapp lactase deficiency or glucose galactose malabsorption problems should not use this medicine.

This medicinal product contains less than 1 mmol (23 mg) sodium per film-coated tablet. No sodium-related side effects are expected at this dose.

4.5. Interactions with other medicinal products and other forms of interaction

No interaction studies with otilonium bromide and other medicines have been performed. It appears that the effect of the use of otilonium bromide at the recommended dose of 40 mg 2 or 3 times daily on the total gastrointestinal transit time is not related to the absorption of other concomitant medicinal products taken orally.

Additional information on special populations:

No interaction studies with otilonium bromide and other drugs have been performed

Pediatric population

No interaction studies have been conducted.

4.6 Pregnancy and lactation**General advice:**

Pregnancy category B

Women of childbearing potential/ Contraception

Since systemic absorption of SPANOL® is very low, the potential for interaction with contraceptives is not expected. To date, no interactions in this regard have been reported in clinical use.

Pregnancy period

No clinical data on exposure during pregnancy are available for SPANOL®. Animal studies do not indicate direct or indirect harmful effects in relation to pregnancy/embryonal/fetal development/birth or postnatal development (see section 5.3). Caution should be exercised when administering to pregnant women.

Lactation period

SPANOL® should be used in nursing mothers only in compulsory cases and under the supervision of a physician.

Reproductive ability / Fertility

No effect on fertility has been observed or is expected.

4.7 Effects on the use of vehicles and machinery

No effects of SPANOL® on the ability to drive and use machines have been reported to date.

4.8 Undesirable effects

In clinical trials with otilonium bromide, the drug was well tolerated, the number of reports of adverse effects was very small and attributable to adverse effects reported in the placebo/reference drug groups (see table below).

The following terms were used to classify adverse reactions: very common ($\geq 1/10$) (common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); Unknown (cannot be estimated from available data).

Nervous system diseases	Uncommon: Headache
Ear and inner ear diseases	Uncommon: Vertigo
Gastrointestinal diseases	Uncommon Dry mouth Nausea Upper abdominal pain
Skin and subcutaneous tissue diseases	Uncommon Prurit Eritem
General disorders and application site related diseases	Uncommon fatigue weakness

In post-marketing experience, there have been isolated reports of skin hypersensitivity reactions (urticaria, angioedema). As these reactions were obtained from a population of indeterminate size and reported voluntarily, it is not possible to reliably assess their frequency and therefore are unknown.

In addition, adverse effects were also noted in a placebo-controlled clinical trial with SPANOL®. However, these effects (nausea, epigastric pain, vomiting) did not occur with a higher frequency than placebo and were mainly due to gastrointestinal flora.

Reporting of side effects:

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also 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 and treatment

In animals, otilonium bromide has been shown to have virtually no toxic effects when used at doses many times the normal pharmacological dose (see section 5.3). Therefore, there have been no special problems due to overdose in humans. In case of overdose, symptomatic and supportive treatment should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in functional gastrointestinal disorders, synthetic anticholinergic agents, quaternary ammonium compounds

ATC kodu: A03AB06

Otilonium bromide is a prototype of the quaternary salts of 2-aminoethyl-N- benzoylamino-benzoate.

Otilonium bromide exerts a strong antispastic effect on the smooth muscles of the digestive tract.

Mechanism of action: otilonium bromide can alter Ca^{2+} influx mainly from cellular and extracellular sites and thus decreases contractile activity. It inhibits L-type Ca channels and Ca^{2+} ions enter through intestinal smooth muscle. Additional pharmacodynamic effects are achieved by inhibition of muscarinic and tachykinin receptors.

Pharmacodynamic effects: Otilonium bromide has antispastic effects on smooth muscles in the distal parts of the colon and rectum. At the doses at which this effect is observed, it does not affect gastric secretion and the occurrence of typical atropine-like adverse effects.

Clinical efficacy and safety: Extended analyses of double-blind, placebo-controlled, 15-week studies of otilonium bromide in 378 IBS patients showed that the rate of responses was significantly higher in patients treated with otilonium bromide for 2-4 months (36.9%) than in the placebo group (22.5%- $P=0.007$). The monthly response rate in each month of treatment was higher in the otilonium bromide group compared with the placebo group ($P<0.05$). The overall monthly and weekly single endpoint (frequency and intensity of discomfort and pain, meteorism/abdominal bloating, severity of diarrhea and constipation, and mucus in feces) treatment responses of the population were greater in the otilonium bromide-treated group than in the placebo-treated group by 10% to 20%. The results of the frequency of failures in subgroups and the density of feces indicate that additional benefits were also achieved in

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patients with diarrhea. Safety conclusions about the use of otilonium bromide overlap with those of placebo. Recent large double-blind and placebo-controlled clinical trials confirm that

otilonium bromide is more effective than placebo in reducing the frequency of abdominal pain, the severity of abdominal discomfort and preventing recurrence of symptoms..

5.2. Pharmacokinetic properties

General features:

Absorption

Otilonium bromide probably comes through the intestinal wall directly to the site of pharmacologic action. Systemic absorption after oral administration is very low (3%). Therefore, its plasma concentration is low.

Dispersion

After oral administration, the drug has been shown to be highly distributed in the smooth muscles of the colon and rectum.

Biotransformation

Taking the drug shortly before eating provides pharmacologically effective local bioavailability at the site of the therapeutic effect and at the expected time the most pronounced symptoms of the disease

Elimination

Most of the absorbed drug is excreted in bile.

Linearity/non-linearity:

As the drug is not absorbed systemically, linearity cannot be assessed.

Characteristics of the patients

Otilonium bromide has not been studied in patients with renal and hepatic impairment. Since otilonium bromide passes very little into the systemic circulation when used orally, reduced renal and hepatic function is not expected to alter the local effect of otilonium bromide.

5.3. Preclinical safety data

Acute toxicity: LD50 for rats 1500 mg/kg, no fatal cases have been reported when given to dogs at a dose of 1000 mg/kg.

Chronic toxicity: In animal studies, no histologic or hematologic abnormalities were observed after 180 days of otilonium bromide at a dose of 80/mg/kg.

Teratogenicity: No embryotoxic and teratogenic effects were observed when given to rats and rabbits at doses of 60 mg/kg.

Mutagenicity: Standard in vivo and in vitro tests have shown no mutagenic effects.

6 PHARMACEUTICAL PROPERTIES

6.1. List of excipients

- Lactose monohydrate (bovine origin)
- Corn starch
- Sodium starch glycolate
- Magnesium
- Hypromellosis
- Titanium dioxide (E171)
- Talk
- Polyethylene glycol

6.2. Incompatibilities

Unknown

6.3. Shelf life

36 months

6.4. Special for storage

Stored at room temperature below 25 C. °

6.5. Nature and content of packaging

PVC /PE / PVDC-Al foil blister pack containing 30 and 90 film-coated tablets, supplied in a cardboard box with instructions for use.

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

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7 MARKETING AUTHORISATION HOLDER

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0212 220 64 00
0212 222 57 59

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

[To be completed nationally]