SUMMARY OF PRODUCT CHARACTERISTICS

SPASMEX® 30 mg film-coated tablets
SPASMEX® 15 mg film-coated tablets.

1. NAME OF THE MEDICINAL PRODUCT

Spasmex® 30 film-coated tablets
Spasmex® 15 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet of Spasmex 30 contains 30 mg trospium chloride.
1 film-coated tablet of Spasmex 15 contains 15 mg trospium chloride.
Excipients with known effect: 1 film-coated tablet contains 100 mg lactose-monohydrate
For the complete list of excipients see chapter 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Spasmex 30: White, round, biconvex film-coated tablets with a special score line ("SNAP-TAB") on one side. The tablet may be divided into two equal doses.

Spasmex 15: White, round, biconvex film-coated tablets, special score line ("SNAP-TAB") on one side and the stamp "0" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of vegetative bladder dysfunction accompanied by urgency and/or frequency and/or urinary incontinence.

4.2 Posology and method of administration

15 mg (one tablet of Spasmex 15 or half a tablet of Spasmex 30) should be taken three times a day, or 30 mg in the morning (two tablets of Spasmex 15 or one tablet of Spasmex 30) and 15 mg in the evening.

Patients with reduced kidney function

In patients with severely impaired renal function (Creatinine clearance between 10 and 30 ml/ min/ 1.73 m^2) a daily dose of 15 mg should not be exceeded.

Patients with reduced liver function

Dose adjustment does not appear necessary in patients with a mild to moderate impairment in liver function (Child-Pugh 5-6 or 7-9) (see section 5.2 Pharmacokinetic properties).

Studies for patients with severe liver dysfunction (Child-Pugh > 10; class C) have not been carried out meaning that treatment cannot be recommended in these cases.

Use in children

Treatment in children under 12 years old is not recommended as no data exist.

Mode and duration of treatment

The film-coated tablets should be swallowed whole with a sufficient quantity of liquid before a meal on an empty stomach. The necessity of a continuation of treatment should be monitored at regular intervals of 3 – 6 months.

4.3 Contraindications

- hypersensitivity to the active substance trospium chloride or to any of the excipients listed in section 6.1
- urinary retention
- narrow-angle glaucoma
- tachyarrhythmia
- myasthenia gravis
- severe chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease)
- toxic megacolon
- renal impairment requiring dialysis (Creatinine clearance < 10 ml/ min/ 1.73 m^2)

4.4 Special warnings and special precautions for use

Special care should be taken with trospium chloride in patients with

- an obstruction in the gastro-intestinal tract (e.g. pyloric stenosis)
- obstructed passage of urine outflow with the risk of residual urine
- autonomous neuropathy
- hiatus hernia with reflux esophagitis
- as well as in patients where a fast heart rate is not desired e.g. those with thyroid hyperactivity, coronary heart disease and heart insufficiency

As no data exist regarding use of trospium chloride in patients with severe liver dysfunction, use in these patients is not recommended. Caution should be taken in patients with mild to moderate impairment in liver function.

Trospium chloride is mainly excreted via the kidneys. In patients with severely impaired renal function notable increases in plasma levels were observed. Therefore in this patient group, even by only mild to moderately impaired kidney function, treatment should only be commenced with caution.

Before starting treatment, organic causes for pollakisuria and urge symptomatology, such as heart or kidney disorders, polydipsia, as well as infections and tumors in the urinary organs should be excluded.

Patients suffering from the rarely observed hereditary galactose intolerance, lactase deficiency or glucose-galactose-malabsorption should not take Spasmex.

Children

Spasmex is not recommended for children under 12 years of age.

4.5 Interaction with other medicinal products and other forms of interaction The following interactions may occur:

- Increase in the anticholinergic effect of amantadine, tricyclic antidepressants, quinidine, antihistamines and disopyramide as well as an
- Increase in the tachycardic effect of ß-sympathomimetics
- Decrease in the effect of prokinetics (e.g. metoclopramid and cisaprid).

Because trospium chloride influences the gastro-intestinal motility and secretion it cannot be ruled out that the ingestion of concurrently taken drugs will not be changed.

During concurrent intake of medicines that contain substances such as guar, colestyramine and colestipol, it cannot be ruled out that the resorption of trospium chloride will not be reduced. Therefore the concurrent use of medications which contain these substances is not recommended.

Investigations into metabolic interactions connected with trospium chloride were examined in vitro using cytochrome P-450 enzymes which are involved in the metabolism of drug substances (P450 1A2, 2A6, 2C6, 2C9, 2C19, 2D6, 2E1, 3A4). No influence by trospium chloride on the metabolic activities could be shown. Due to the fact that trospium chloride is only metabolised to a small extent, and that an ester hydrolysis represents the only relevant metabolic pathway, no interactions as a consequence of metabolism are to be expected.

In addition, neither clinical studies nor pharmacovigilance have revealed data which indicate clinically relevant interactions.

4.6 Fertility, pregnancy and lactation Fertility

There are no human data available. Animal studies do not indicate a risk of impaired fertility. In animal studies no evidence has been found that trospium chloride has a directly or indirectly harmful influence on pregnancy, embryonic/ foetal development, delivery or postnatal development (see chapter 5.3). Nonetheless, Spasmex should only be used during pregnancy or when breast-feeding after close examination of the indication due to the lack of experience with this drug in humans during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Due to accommodation disturbances the ability to drive or operate machines may be impaired.

4.8 Undesirable effects

Side effects observed during treatment with trospium chloride are mainly caused by the typical anticholinergic effect such as dry mouth dyspepsia or constipation.

In a controlled clinical study involving 30 mg trospium chloride, the following side effects with at frequency of ≥ 1% were observed with at least a possible causal connection: dry mouth (4.1%), stomach ache (2.4%), constipation (2.1%), nausea (1.2%), dizziness (1.2%) and headache (1.1%).

Following market launch of trospium chloride containing medicines, the side effects in the following table were observed according to the shown frequencies and system organ classes:

System organ class	**common** (≥ 1/10) **Very**	**Common** (≥1/100 to <1/10)	**Uncommon** (≥ 1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Not known** (cannot be estimated from the available data)
Immune system disorders.				Anaphylaxis	StevensJohnson Syndrome (SJS), toxic epidermal necrolyses (TEN)
Eye disorders			Accommodation disorders (especially in patients who are hyperopic and not sufficiently corrected)		
Cardiac disorders			Tachycardia	Tachyarrhythmia	
Respiratory, thoracic and mediastinal disorders				Dyspnoea	
Gastrointestinal disorders	Dry mouth,	Dyspepsia, constipation, stomach ache and nausea	Diarrhoea, flatulence		
Skin and subcutaneous tissue disorders			Skin rashes	Angioedema	
Renal and urinary tract disorders			Disturbance in urination (e.g. formation of residual urine)	Urinary retention	
General disorders and administration site conditions			Weakness or chest pains		
Investigations				Mild to moderate increase of transaminases	

The following undesirable effects have additionally been observed in other products containing trospium chloride: dry eyes, disturbed vision, dry nose, urinary tract infection, myalgia and arthralgia.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

The highest single dose of trospium chloride which has been given to humans orally is 360 mg. Dry mouth, tachycardia and micturition disturbances were observed. Cases of severe overdose or intoxication with trospium chloride have not been reported up till now.

Expected signs of an overdose are increased anticholinergic symptoms such as visual disturbances, tachycardia, a dry mouth and reddening of the skin.

Upon presentation of an overdose, the following measured should be taken:

- gastric lavage and impairment of resorption (e.g. activated charcoal)
- local application of pilocarpine in patients with glaucoma
- catheterisation by urinary retention
- Administration of a parasympathomimetic in severe cases (e.g. neostigmine).
- Administration of beta-ß-blockers in cases of insufficient response, manifest tachycardia and/ or circulatory instability (e.g. starting with 1 mg Propanolol i.v. under ECG and blood pressure surveillance).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antispasmodic urological including drug

ATC code: G04B D09

Trospium chloride, a quaternary ammonium derivative of nortropanol belongs to the group of parasympatholytic or anticholinergic compounds. Depending on the concentration, the drug competes with the endogenous transmitter acetylcholine for postsynaptic binding sites. The drug has a high affinity for the M1 - and M3-receptors and in comparison a lower affinity for the M2-receptor and binds to nicotinic receptors at a negligibly low rate.

Trospium chloride has a considerable relaxing effect on smooth muscles and organs due to its antimuscarinic properties which are transmitted through the muscarine receptors.

Trospium chloride reduces the tension of the smooth muscles in the gastrointestinal and urogenital tract. It inhibits the bronchial, salivary and sweat secretion and paralyses accommodation. Central effects have not been observed up till now.

In two specific safety studies in healthy volunteers trospium chloride has been proven not to affect cardiac repolarisation, but has been shown to have a consistent and dose dependent heart rate accelerating effect.

5.2 Pharmacokinetic properties

Maximal blood levels of trospium chloride are reached four to six hours following oral administration. The elimination half-life is very variable and ranges between 5 and 18 hours after oral application. There is no accumulation. The plasma protein binding rate is 50-80%.In the dose range of 20 to 60 mg as single dose the plasma levels are linear to the applied dose. The predominant portion of systemically available trospium chloride is excreted largely unchanged via the renal system. A small portion is excreted as spiro-alcohol (ca. 10%), a metabolite formed by hydrolysis of the ester.

<u>Special patient groups</u>

Pharmacokinetic data did not reveal any major differences in elderly patients or between genders.

Simultaneous food intake results in reduced bioavailability but more homogenous plasma levels. With the knowledge that equivalence of efficacy of trospium chloride immediate release formulations

has been proven compared to oxybutynin, without prescribing ingestion under fasting conditions, there is no need to take Spasmex film-coated tablets under fasting conditions.

Trospium chloride exhibits diurnal variability in exposure with decrease in both Cmax and AUC for lunchtime and evening in relation to morning doses.

In a study involving patients suffering from moderate to severe renal impairment (Cockcroft-Gault formula estimated creatinine clearance < 50 mL/ min) the mean AUC was found to be 5-fold and the Cmax to be 4.5-fold increased. The half-life was prolonged (1.7-fold) in comparison to healthy persons. No marked differences with regard to AUC and Cmax were found between healthy subjects and patients with mild renal impairment (creatinine clearance 50-80 mL / min).

Results from a pharmacokinetic study on patients with mild to moderate impairment in live function did not reveal the necessity of dose adjustment in this group of patients.

5.3 Preclinical safety data

Toxicological properties

a) Mutagenic and carcinogenic potential

Trospium chloride showed no mutagenic effects *in-vitro and in-vivo.* Long-term carcinogenic studies involving rats and mice provided no evidence of carcinogenic potential. *b) Reproductive toxicity*

Embryo toxicity studies carried out on rats and rabbits provided no evidence of teratogenic or other embryotoxic effects. Fetal development, parturition, postnatal development of the offspring and fertility of the rats were not impaired.

In rats, trospium chloride passes the placental barrier and is excreted into the breast milk. Experience of use in humans during pregnancy and lactation does not exist.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate Type A, hypromellose, lactose monohydrate, maize starch, microcrystalline cellulose; povidone K25; colloidal anhydrous silica; stearic acid, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/Aluminium blisters with 10 film-coated tablets, 30 film coated tablets, and 100 film coated tablets.

6.6 Special precautions for disposal None

7. MARKETING AUTHORIZATION HOLDER

TEC-O-PHARM-LIBRA LTD POB 45054, JERUSALEM 91450

8. MARKETING AUTHORIZATION NUMBER

Spasmex 30: 142-14-31805

Spasmex 15: 132-49-30583

9. SALES STATUS

Prescription only medicine.

Revised in June 2021 according to MOHs guidelines