Toviaz® 4 mg
Toviaz® 8 mg

1. NAME OF THE MEDICINAL PRODUCT

TOVIAZ 4 mg sustained release tablets
TOVIAZ 8 mg sustained release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TOVIAZ 4 mg tablets
Each sustained release tablet contains fesoterodine fumarate 4 mg corresponding to 3.1 mg of fesoterodine.

TOVIAZ 8 mg tablets
Each sustained release tablet contains fesoterodine fumarate 8 mg corresponding to 6.2 mg of fesoterodine.

Excipients with known effect

TOVIAZ 4 mg tablets
Each 4 mg sustained release tablet contains 0.525 mg of soya lecithin and 91.125 mg of lactosemonohydrate.

TOVIAZ 8 mg tablets
Each 8 mg sustained release tablet contains 0.525 mg of soya lecithin and 58.125 mg of lactosemonohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sustained release tablet.

TOVIAZ 4 mg tablets
The 4 mg tablets are light blue, oval, biconvex, film-coated, and engraved on one side with the letters ‘FS’.

TOVIAZ 8 mg tablets
The 8 mg tablets are blue, oval, biconvex, film-coated, and engraved on one side with the letters ‘FT’.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome.

4.2 Posology and method of administration

Posology

Adults (including elderly)
The recommended starting dose is 4 mg once daily. Based upon individual response, the dose may be increased to 8 mg once daily. The maximum daily dose is 8 mg.

Full treatment effect was observed between 2 and 8 weeks. Hence, it is recommended to re-evaluate the efficacy for the individual patient after 8 weeks of treatment.

In subjects with normal renal and hepatic function receiving concomitant administration of potent CYP3A4 inhibitors, the maximum daily dose of TOVIAZ should be 4 mg once daily (see section 4.5).

Special population

Renal and hepatic impairment
The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of moderate and potent CYP3A4 inhibitors (see sections 4.3, 4.4, 4.5 and 5.2).

		Moderate[3] or potent[4] CYP3A4 inhibitors		
		None	Moderate	Potent
Renal impairment[1]	Mild	4→8 mg[2]	4 mg	Should be avoided
	Moderate	4→8 mg[2]	4 mg	Contraindicated
	Severe	4 mg	Should be avoided	Contraindicated
Hepatic impairment	Mild	4→8 mg[2]	4 mg	Should be avoided
	Moderate	4 mg	Should be avoided	Contraindicated

(1) Mild GFR = 50-80 ml/min; Moderate GFR = 30-50 ml/min; Severe GFR = <30 ml/min
(2) Cautious dose increase. See sections 4.4, 4.5 and 5.2
(3) Moderate CYP3A4 inhibitors. See section 4.5
(4) Potent CYP3A4 inhibitors. See sections 4.3, 4.4 and 4.5

TOVIAZ is contraindicated in subjects with severe hepatic impairment (see section 4.3).

Paediatric population
The safety and efficacy of TOVIAZ in children below 18 years of age have not yet been established. No data are available.

Method of administration
Tablets are to be taken once daily with liquid and swallowed whole. TOVIAZ can be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to peanut or soya or to any of the excipients listed in section 6.1
- Urinary retention
- Gastric retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- Severe hepatic impairment (Child Pugh C)
- Concomitant use of potent CYP3A4 inhibitors in subjects with moderate to severe hepatic or renal impairment
- Severe ulcerative colitis
- Toxic megacolon.

4.4 Special warnings and precautions for use

TOVIAZ should be used with caution in patients with:

- Clinically significant bladder outflow obstruction at risk of urinary retention (e.g. clinically significant prostate enlargement due to benign prostatic hyperplasia, see section 4.3)
- Gastrointestinal obstructive disorders (e.g. pyloric stenosis)

- Gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as oral bisphosphonates) that can cause or exacerbate oesophagitis
- Decreased gastrointestinal motility
- Autonomic neuropathy
- Controlled narrow-angle glaucoma

Caution should be exercised when prescribing or uptitrating fesoterodine to patients in whom an increased exposure to the active metabolite (see section 5.1) is expected:

- Hepatic impairment (see sections 4.2, 4.3 and 5.2)
- Renal impairment (see sections 4.2, 4.3 and 5.2)
- Concomitant administration of potent or moderate CYP3A4 inhibitors (see sections 4.2 and 4.5)
- Concomitant administration of a potent CYP2D6 inhibitor (see sections 4.5 and 5.2).

Dose increases
In patients with a combination of these factors, additional exposure increases are expected. Dose dependent antimuscarinic adverse reactions are likely to occur. In populations where the dose may be increased to 8 mg once daily, the dose increase should be preceded by an evaluation of the individual response and tolerability.

Organic causes must be excluded before any treatment with antimuscarinics is considered. Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Other causes of frequent urination (treatment of heart failure or renal disease) should be assessed before treatment with fesoterodine. If urinary tract infection is present, an appropriate medical approach should be taken/antibacterial therapy should be started.

Angioedema
Angioedema has been reported with fesoterodine and has occurred after the first dose in some cases. If angioedema occurs, fesoterodine should be discontinued and appropriate therapy should be promptly provided.

Potent CYP3A4 inducers
The concomitant use of fesoterodine with a potent CYP3A4 inducer (i.e. carbamazepine, rifampicin, phenobarbital, phenytoin, St John's Wort) is not recommended (see section 4.5).

QT prolongation
TOVIAZ should be used with caution in patients with risk for QT prolongation (e.g. hypokalaemia, bradycardia and concomitant administration of medicines known to prolong QT interval) and relevant pre-existing cardiac diseases (e.g. myocardial ischaemia, arrhythmia, congestive heart failure), (see section 4.8). This especially holds true when taking potent CYP3A4 inhibitors (see sections 4.2, 4.5 and 5.1).

Lactose
TOVIAZ prolonged-release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacological interactions
Caution should be exercised in coadministration of fesoterodine with other antimuscarinics and medicinal products with anticholinergic properties (e.g. amantadine, tri-cyclic antidepressants, certain neuroleptics) as this may lead to more pronounced therapeutic- and side-effects (e.g. constipation, dry mouth, drowsiness, urinary retention).
Fesoterodine may reduce the effect of medicinal products that stimulate the motility of the gastro-intestinal tract, such as metoclopramide.

Pharmacokinetic interactions
In vitro data demonstrate that the active metabolite of fesoterodine does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant plasma concentrations. Thus fesoterodine is unlikely to alter the clearance of medicinal products that are metabolised by these enzymes.

CYP3A4 inhibitors

Potent CYP3A4 inhibitors
Following inhibition of CYP3A4 by co-administration of ketoconazole 200 mg twice daily, C_{max} and AUC of the active metabolite of fesoterodine increased 2.0 and 2.3-fold in CYP2D6 extensive metabolisers and 2.1 and 2.5-fold in CYP2D6 poor metabolisers, respectively. Therefore, the maximum dose of fesoterodine should be restricted to 4 mg when used concomitantly with potent CYP3A4 inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir (and all ritonavir boosted PI-regimens), saquinavir and telithromycin (see sections 4.2 and 4.4)).

Moderate CYP3A4 inhibitors
Following blockade of CYP3A4 by coadministration of the moderate CYP3A4 inhibitor fluconazole 200 mg twice a day for 2 days, C_{max} and AUC of the active metabolite of fesoterodine increased approximately 19% and 27%, respectively. No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil and grapefruit juice).

Weak CYP3A4 inhibitors
The effect of weak CYP3A4 inhibitors (e.g. cimetidine), was not examined; it is not expected to be in excess of the effect of moderate inhibitor.

CYP3A4 inducers
Following induction of CYP3A4 by coadministration of rifampicin 600 mg once a day, C_{max} and AUC of the active metabolite of fesoterodine decreased by approximately 70% and 75%, respectively, after oral administration of fesoterodine 8 mg.

Induction of CYP3A4 may lead to subtherapeutic plasma levels. Concomitant use with CYP3A4 inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin, St John's Wort) is not recommended (see section 4.4).

CYP2D6 inhibitors
The interaction with CYP2D6 inhibitors was not tested clinically. Mean C_{max} and AUC of the active metabolite are 1.7 and 2-fold higher, respectively, in CYP2D6 poor metabolisers as compared to extensive metabolisers. Co-administration of a potent CYP2D6 inhibitor may result in increased exposure and adverse events. A dose reduction to 4 mg may be needed (see section 4.4).

Oral contraceptives
Fesoterodine does not impair the suppression of ovulation by oral hormonal contraception. In the presence of fesoterodine there are no changes in the plasma concentrations of combined oral contraceptives containing ethinylestradiol and levonorgestrel.

Warfarin
A clinical study in healthy volunteers has shown that fesoterodine 8 mg once daily has no significant effect on the pharmacokinetics or the anticoagulant activity of a single dose of warfarin.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of fesoterodine in pregnant women. Reproductive toxicity studies with fesoterodine in animals show minor embryotoxicity. In animal reproduction studies, oral administration of fesoterodine to pregnant mice and rabbits during organogenesis resulted in fetotoxicity at maternal exposures that were 6 and 3 times the maximum recommended human dose (MRHD), respectively, based on AUC (see section 5.3). The potential risk for humans is unknown. TOVIAZ is not recommended during pregnancy.

Breast-feeding

It is unknown whether fesoterodine/metabolites are excreted into human milk; therefore, breast-feeding is not recommended during treatment with TOVIAZ.

Fertility

No clinical trials have been conducted to assess the effect of fesoterodine on human fertility. Findings in mice at exposures approximately 5 to 19 times those at the MRHD show an effect on female fertility, however, the clinical implications of these animal findings are not known (see section 5.3). Women of child bearing potential should be made aware of the lack of human fertility data, and TOVIAZ should only be given after consideration of individual risks and benefits.

4.7 Effects on ability to drive and use machines

TOVIAZ has minor influence on the ability to drive and use machines.

Caution should be exercised when driving or using machines due to possible occurrence of side effects such as blurred vision, dizziness, and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of fesoterodine was evaluated in placebo-controlled clinical studies in a total of 2859 patients with overactive bladder, of which 780 received placebo.

Due to the pharmacological properties of fesoterodine, treatment may cause mild to moderate antimuscarinic effects like dry mouth, dry eye, dyspepsia and constipation. Urinary retention may occur uncommonly.

Dry mouth, the only very common adverse reactions, occurred with a frequency of 28.8% in the fesoterodine group compared to 8.5% in the placebo group. The majority of adverse reactions occurred during the first month of treatment with the exception of cases classified as urinary retention or post void residual urine greater than 200 ml, which could occur after long term treatment and was more common in male than female subjects.

Tabulated list of adverse reactions

The table below gives the frequency of treatment emergent adverse reactions from placebo-controlled clinical trials and from post-marketing experience. The adverse reactions are reported in this table with the following frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare
Infections and infestations			Urinary tract infection	
Psychiatric disorders		Insomnia		Confusional state

System organ class	Very common	Common	Uncommon	Rare
Nervous system disorders		Dizziness; Headache	Dysgeusia; Somnolence	
Eye disorders		Dry eye	Blurred vision	
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Tachycardia; Palpitations	
Respiratory, thoracic and mediastinal disorders		Dry throat	Pharyngolaryngeal pain; Cough; Nasal dryness	
Gastrointestinal disorders	Dry mouth	Abdominal pain; Diarrhoea; Dyspepsia; Constipation; Nausea	Abdominal discomfort; Flatulence, Gastroesophageal reflux	
Hepatobiliary disorders			ALT increased; GGT increased	
Skin and subcutaneous tissue disorders			Rash; Dry skin; Pruritus	Angioedema; Urticaria
Renal and urinary disorders		Dysuria	Urinary retention (including feeling of residual urine; micturition disorder); Urinary hesitation	
General disorders and administration site conditions			Fatigue	

Description of selected adverse reactions

In clinical trials of fesoterodine, cases of markedly elevated liver enzymes were reported with the occurrence frequency no different from the placebo group. The relation to fesoterodine treatment is unclear.

Electrocardiograms were obtained from 782 patients treated with 4 mg, 785 treated with 8 mg, 222 treated with 12 mg fesoterodine and 780 with placebo. The heart rate corrected QT interval in fesoterodine treated patients did not differ from that seen in placebo treated patients. The incidence rates of QTc ≥500 ms post baseline or QTc increase of ≥60 ms is 1.9%, 1.3%, 1.4% and 1.5%, for fesoterodine 4 mg, 8 mg, 12 mg and placebo, respectively. The clinical relevance of these findings will depend on individual patient risk factors and susceptibilities present (see section 4.4).

Post-marketing cases of urinary retention requiring catheterisation have been described, generally within the first week of treatment with fesoterodine. They have mainly involved elderly (≥ 65 years) male patients with a history consistent with benign prostatic hyperplasia (see section 4.4).

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

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

4.9 Overdose

Overdose with antimuscarinics, including fesoterodine can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdose, ECG monitoring is recommended; standard supportive measures for managing QT prolongation should be adopted. Fesoterodine has been safely administered in clinical studies at doses up to 28 mg/day.

In the event of fesoterodine overdose, treat with gastric lavage and give activated charcoal. Treat symptoms as follows:

- Severe central anticholinergic effects (e.g. hallucinations, severe excitation): treat with physostigmine
- Convulsions or pronounced excitation: treat with benzodiazepines
- Respiratory insufficiency: treat with artificial respiration
- Tachycardia: treat with beta-blockers
- Urinary retention: treat with catheterisation
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Urinary antispasmodics, ATC code: G04BD11.

Mechanism of action
Fesoterodine is a competitive, specific muscarinic receptor antagonist. It is rapidly and extensively hydrolysed by non-specific plasma esterases to the 5-hydroxymethyl derivative, its primary active metabolite, which is the main active pharmacological principle of fesoterodine.

Clinical efficacy and safety
The efficacy of fixed doses of fesoterodine 4 mg and 8 mg was evaluated in two Phase 3 randomised, double-blind, placebo-controlled, 12-week studies. Female (79%) and male (21%) patients with a mean age of 58 years (range 19-91 years) were included. A total of 33% of patients were ≥65 years of age and 11% were ≥75 years of age.

Fesoterodine treated patients had statistically significant mean reductions in the number of micturitions per 24 hours and in the number of urge incontinence episodes per 24 hours at the end of treatment compared to placebo. Likewise, the response rate (% of patients reporting that their condition has been “greatly improved” or “improved” using a 4-point Treatment Benefit Scale) was significantly greater with fesoterodine compared to placebo. Furthermore, fesoterodine improved the mean change in the voided volume per micturition, and the mean change in the number of continent days per week (see Table 1 below).

Table 1: Mean changes from Baseline to end of treatment for primary and selected secondary endpoints

	Study 1				Study 2		
Parameter	**Placebo**	**Fesoterodine 4 mg**	**Fesoterodine 8 mg**	**Active comparator**	**Placebo**	**Fesoterodine 4 mg**	**Fesoterodine 8 mg**
Number of micturitions per 24 hours#							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Baseline	12.0	11.6	11.9	11.5	12.2	12.9	12.0
Change from baseline	-1.02	-1.74	-1.94	-1.69	-1.02	-1.86	-1.94
p-value		<0.001	<0.001			0.032	<0.001

Responder rate (treatment response)#							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Responder rate	53.4%	74.7%	79.0%	72.4%	45.1%	63.7%	74.2%
p-value		<0.001	<0.001			<0.001	<0.001
Number of urge incontinence episodes per 24 hours							
	N=211	N=199	N=223	N=223	N=205	N=228	N=218
Baseline	3.7	3.8	3.7	3.8	3.7	3.9	3.9
Change from baseline	-1.20	-2.06	-2.27	-1.83	-1.00	-1.77	-2.42
p-value		0.001	<0.001			0.003	<0.001
Number of continent days per week							
	N=211	N=199	N=223	N=223	N=205	N=228	N=218
Baseline	0.8	0.8	0.6	0.6	0.6	0.7	0.7
Change from baseline	2.1	2.8	3.4	2.5	1.4	2.4	2.8
p-value		0.007	<0.001			<0.001	<0.001
Voided volume per micturition (ml)							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Baseline	150	160	154	154	159	152	156
Change from baseline	10	27	33	24	8	17	33
p-value		<0.001	<0.001			0.150	<0.001

primary end points

Cardiac electrophysiology

The effect of fesoterodine 4 mg and 28 mg on the QT interval was thoroughly evaluated in a double-blind, randomised, placebo- and positive-controlled (moxifloxacin 400 mg) parallel group study with once-daily treatment over a period of 3 days in 261 male and female subjects aged 45 to 65 years. Change from baseline in QTc based on the Fridericia correction method did not show any differences between the active treatment and placebo group.

5.2 Pharmacokinetic properties

Absorption

After oral administration, due to rapid and extensive hydrolysis by non-specific plasma esterases, fesoterodine was not detected in plasma.

Bioavailability of the active metabolite is 52%. After single or multiple-dose oral administration of fesoterodine in doses from 4 mg to 28 mg, plasma concentrations of the active metabolite are proportional to the dose. Maximum plasma levels are reached after approximately 5 hours. Therapeutic plasma levels are achieved after the first administration of fesoterodine. No accumulation occurs after multiple-dose administration.

Distribution

Plasma protein binding of the active metabolite is low with approximately 50% bound to albumin and alpha-1-acid glycoprotein. The mean steady-state volume of distribution following intravenous infusion of the active metabolite is 169 l.

Biotransformation
After oral administration, fesoterodine is rapidly and extensively hydrolysed to its active metabolite. The active metabolite is further metabolised in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolite with involvement of CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine. Mean C_{max} and AUC of the active metabolite are 1.7 and 2-fold higher, respectively, in CYP2D6 poor metabolisers as compared to extensive metabolisers.

Elimination
Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite. After oral administration of fesoterodine, approximately 70% of the administered dose was recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) was recovered in faeces. The terminal half-life of the active metabolite following oral administration is approximately 7 hours and is absorption rate-limited.

Age and gender
No dose adjustment is recommended in these subpopulations. The pharmacokinetics of fesoterodine are not significantly influenced by age and gender.

Paediatric population
The pharmacokinetics of fesoterodine have not been evaluated in paediatric patients.

Renal impairment
In patients with mild or moderate renal impairment (GFR 30 – 80 ml/min), C_{max} and AUC of the active metabolite increased up to 1.5 and 1.8-fold, respectively, as compared to healthy subjects. In patients with severe renal impairment (GFR < 30 ml/min), C_{max} and AUC are increased 2.0 and 2.3-fold, respectively.

Hepatic impairment
In patients with moderate hepatic impairment (Child Pugh B), C_{max} and AUC of the active metabolite increased 1.4 and 2.1-fold, respectively, as compared to healthy subjects. Pharmacokinetics of fesoterodine in patients with severe hepatic impairment have not been studied.

5.3 Preclinical safety data

In non-clinical safety pharmacology, general toxicity, genotoxicity and carcinogenicity studies no clinically relevant effects have been observed, except those related to the pharmacological effect of the active substance.

Reproduction studies have shown minor embryotoxicity at doses close to maternally toxic ones (increased number of resorptions, pre-implantation and post-implantation losses).

Supratherapeutic concentrations of the active metabolite of fesoterodine, have been shown to inhibit K^+ current in cloned human ether-à-go-go-related gene (hERG) channels and prolong action potential duration (70% and 90% repolarisation) in canine isolated Purkinje fibres. However in conscious dogs, the active metabolite had no effect on the QT interval and QTc interval at plasma exposures at least 33-fold higher than mean peak free plasma concentration in human subjects who are extensive metabolisers and 21-fold higher than measured in subjects who are poor CYP2D6 metabolisers after fesoterodine 8 mg once daily.

In a study of fertility and early embryonic development in mice, fesoterodine had no effect on male reproductive function or fertility at doses up to 45 mg/kg/day. At 45 mg/kg/day, a lower number of corpora lutea, implantation sites and viable foetuses was observed in female mice administered fesoterodine for 2 weeks prior to mating and continuing through day 7 of gestation. The maternal No-Observed-Effect Level

(NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. Based on AUC, the systemic exposure was 0.6 to 1.5 times higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5 to 9 times higher.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Xylitol
Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Glycerol dibehenate
Talc

Film-coating
Opadry® light blue (4mg) or Opadry® blue (8mg) contains:
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Lecithin
Indigo carmine aluminium lake

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 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

TOVIAZ 4 mg and 8 mg tablets are packed in aluminium-aluminium blisters in cartons containing 7, 14, 28 or 56 tablets.

Not all the pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

R-PHARM Germany GmbH, Illertissen, Germany.

8. LICENSE HOLDER

Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar st., Herzeliya 46725.

The content of this leaflet was approved by the Ministry of Health in October 2013 and updated according to the guidelines of the Ministry of Health in January 2018.