SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
SOLFESIRE 10 mg film coated tablets

2. Qualitative and quantitative composition

Each tablet contains;

Active ingredient:
Solifenacin succinate : 10 mg

Excipient(s):
Lactose Monohydrate (cow's milk): 148.95 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Film coated tablet.

Pale pink coloured, round, biconvex film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications
It is indicated for the increased frequency of urination and severe urination in patients with overactive bladder syndrome and/or symptomatic treatment of compression-type incontinence.

4.2 Posology and method of administration

Posology
Adults, including the elderly
The recommended dose is 5 mg solifenacin succinate once daily. If needed, the dose may beincreased to 10 mg solifenacin succinate once daily.

Frequency and duration of administration
It is administered once daily. SOLFESIRE can be used long-term.

Method of administration
SOLFESIRE should be taken orally and should be swallowed whole with liquids. It can be taken with or without food.

Additional information on special populations:

Patients with renal impairment:
No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance > 30 ml/min). Patients with severe renal impairment (creatinine clearance . 30 ml/min) should be treated with caution and receive no more than 5 mg per day (see Section 5.2 Pharmacokinetic properties).

Patients with hepatic impairment:
No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment (ChildPugh score of 7 to 9) should be treated with caution and receive no more than 5 mg per day (see Section 5.2 Pharmacokinetic properties).

Paediatric population:
The safety and efficacy of SOLFESIRE in children have not yet been established. Therefore, SOLFESIRE should not be used in children.

Geriatric population:
The recommended dose is 5 mg solifenacin succinate once daily. If needed, the dose may be increased to 10 mg solifenacin succinate once daily.

Other:
Potent inhibitors of cytochrome P450 3A4:
The maximum dose of SOLFESIRE should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4inhibitors e.g. ritonavir, nelfinavir, itraconazole (*see Section 4.5 Interaction with other medicinal products and other forms of interaction*).

4.3 Contraindications

Solifenacin is contraindicated in patients with urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow angle glaucoma and in patients at risk for these conditions.

- Patients hypersensitive to the active substance or to any of the excipients (see Section 6.1 List of excipients).
- Patients undergoing haemodialysis (see Section 5.2 Pharmacokinetic properties).
- Patients with severe hepatic impairment (see Section 5.2 Pharmacokinetic properties).
- Patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

When used in combination with drugs that can cause long QT syndrome and Torsade de Pointes, SOLFESIRE may increase the risk of long QT syndrome and Torsades de Pointes. Therefore, SOLFESIRE should not be taken in combination with such drugs.

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

SOLFESIRE, should be used with caution in patients with:
- Clinically significant bladder outflow obstruction at risk of urinary retention,
- Gastrointestinal obstructive disorders,
- Risk of decreased gastrointestinal motility,
- Severe renal impairment (creatinine clearance ≤ 30 ml/min; *see Section 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties*) (doses should not exceed 5 mg for these patients),

- Moderate hepatic impairment (ChildPugh score of 7 to 9; *see Section 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties*) (doses should not exceed 5 mg for these patients),
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (*see Section 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties*).
- Hiatus hernia/gastrooesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- Autonomic neuropathy.

In some patients using solifenacin succinate, airway obstruction and angioedema have been reported.
In case of angioedema, treatment of solifenacin succinate should be discontinued and appropriate treatment and / or necessary precautions should be taken.

Anaphylactic reaction has been reported in some patients using solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued, appropriate treatment and / or measurements should be performed.

Since this product contains lactose, patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this drug.

The maximum effect of SOLFESIRE can be determined at the earliest after 4 weeks.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacological interactions
Concomitant medication with other medicinal products with anticholinergic properties may result in more pronounced therapeutic effects and undesirable effects. An interval of approximately one week should be allowed after stopping treatment with SOLFESIRE, before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may bereduced by concomitant administration of cholinergic receptor agonists.

Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions
In vitro studies have demonstrated that at therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. Therefore, solifenacin is unlikely to alter the clearance of drugs metabolised by these CYP enzymes.

Effect of other medicinal products on the pharmacokinetics of solifenacin
Solifenacin is metabolised by CYP3A4. Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, resulted in a two-fold increase of the AUC of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a threefold increase of the AUC of solifenacin. Therefore, the maximum dose of SOLFESIRE should be restricted to 5 mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole) (see Section 4.2 Posology and method of administration).

The effects of enzyme induction on the pharmacokinetics of solifenacin and its metabolites have not been studied as well as the effect of higher affinity CYP3A4 substrates on solifenacin exposure. Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates with higher affinity (e.g. verapamil, diltiazem) and CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepin).

Additional information on special populations

Renal/Hepatic impairment
Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contraindicated in patients with severe renal impairment or moderate hepatic impairment.

Effect of solifenacin on the pharmacokinetics of other medicinal products:

Oral Contraceptives:
Intake of SOLFESIRE showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin:
Intake of SOLFESIRE did not alter the pharmacokinetics of R-warfarin or S-warfarin or their effect on prothrombin time.

Digoxin:
Intake of SOLFESIRE showed no effect on the pharmacokinetics of digoxin.

Pediatric population
Safety and effectiveness in children have not yet been fully determined. Therefore, solifenacinsuccinate should not be used in children.

4.6 Fertility, pregnancy and lactation

General advice
Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)
No data available for contraception.

Pregnancy
No clinical data are available from women who became pregnant while taking solifenacin. Animal studies do not indicate direct harmful effects on fertility, embryonal / foetal development or parturition (*see Section 5.3 Preclinical safety data* 3). *The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.*

Breast-feeding
No data on the excretion of solifenacin in human milk are available. In mice, solifenacin and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice (*see Section 5.3 Preclinical safety data*). The use of SOLFESIRE shouldtherefore be avoided during breastfeeding.

Fertility
There is no more information about infertility and reproduction, except of information that is given in Pregnancy part.

4.7 Effects on ability to drive and use machines
Since solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue (see section 4.8. Undesirable effects), the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects
Due to the pharmacological effect of solifenacin, SOLFESIRE may cause anticholinergic undesirable effects of (in general) mild or moderate severity. The frequency of anticholinergicundesirable effects is dose related.

The most commonly reported adverse reaction with SOLFESIRE was dry mouth. It occurred in 11% of patients treated with 5 mg once daily, in 22% of patients treated with 10 mg once daily and in 4% of placebotreated patients. The severity of dry mouth was generally mild and did only occasionally lead to discontinuation of treatment. In general, medicinal product compliance was very high (approximately 99%) and approximately 90% of the patients treated with SOLFESIRE completed the full study period of 12 weeks treatment.

Undesirable effects are listed in the following system organ class. Frequencies are defined as:In different organ systems;

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), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations:
Uncommon: Urinary tract infection, cystitis

Immune system diseases:
Unknown: Anaphylactic reaction *

Metabolism and nutritional diseases:
Unknown: Appetite reduction *, hyperkalemia *

Psychiatric diseases:
Very rare: hallucination *, confusion status *
Unknown: Delirium *

Nervous system disorders:
Uncommon: Somnolence, dysgeusia
Very rare: Dizziness, headache

Eye disorders:
Common: Blurred vision
Uncommon: Dry eyes
Unknown: Glaucoma *

Cardiac diseases:
Unknown: Torsades de Pointes *,
QT elongation of electrocardiogram *,

Atrial fibrillation *,
Tachycardia *

Respiratory, thoracic and mediastinal disorders:
Uncommon: Nasal dryness
Unknown: Disfoni *

Gastrointestinal disorders:
Very common: Dry mouth
Common : Constipation, nausea, dyspepsia, abdominal pain Uncmmon : Gastrooesophageal reflux diseases, dry throat Rare : Colonic obstruction, stiffness, vomiting
Unknown: ileus *, abdominal discomfort *

Hepatobiliary diseases:
Unknown: Liver disease, liver function test abnormality *

Skin and subcutaneous tissue disorders:
Uncommon : Dry skin
Rare: Pruritus *, rash *
Very rare: Erythema multiforme *, urticaria *, angioedema *
Unknown: Exfoliative dermatitis *

Musculoskeletal disorders, connective tissue and bone diseases:
Unknown: Muscle weakness *

Kidney and urinary diseases:
Uncommon: Difficult to urinate
Rare: Urinary retention
Unknown: Renal insufficiency *

General disorders and administration site conditions:
Uncommon: Fatigue, peripheral edema

* Post-marketing observed.

4.9 Overdose and treatment

Symptoms
Over dosage of solifenacin succinate may result in severe anticholinergic effect and should betreated appropriately. A maximum dose of 280 mg of solifenacin succinate was given to a patient by mistake for 5 hours. Mental status changes that did not require hospitalization were observed.

Treatment
In case of overdose with solifenacin succinate, the patient should be treated with activated charcoal. Gastric lavage is useful if applied within 1 hour, but the patient should not be vomited.

As with other anticholinergics, the symptoms can be treated as follows:

- Severe central anticholinergic effects such as hallucinations or pronounced excitation: treat with physostigmine or carbachol.
- Convulsions or pronounced excitation: treat with benzodiazepines.

- Respiratory insufficiency: treat with artificial respiration.
- Tachycardia: treat with betablockers.
- Urinary retention: treat with catheterisation.
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room.

As with other antimuscarinics, in case of overdosing, specific attention should be paid to patients with known risk for Qt-prolongation (i.e. hypokalaemia, bradycardia and concurrentadministration of medicinal products known to prolong QT-interval) and relevant preexisting cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure).

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodicsATC code: G04B D08

Mechanism of action:
Solifenacin is a competitive, specific cholinergicreceptor antagonist.

The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M3 subtypeis predominantly involved. In vitro and in vivo pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 subtype receptor. In addition, solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

Pharmacodynamic effects:
Treatment with solifenacin succinate in doses of 5 mg and 10 mg daily was studied in several double blind, randomised, controlled clinical trials in men and women with overactive bladder**.**

As shown in the table below, both the 5 mg and 10 mg doses of solifenacin succinate produced statistically significant improvements in the primary and secondary endpoints compared with placebo. Efficacy was observed within one week of starting treatment and stabilises over a period of 12 weeks. A long term open label study demonstrated that efficacy was maintained for at least 12 months. After 12 weeks of treatment approximately 50% of patients suffering from incontinence before treatment were free of incontinence episodes, and in addition 35% of patients achieved a micturition frequency of less than 8 micturitions per day.

Treatment of the symptoms of overactive bladder also results in a benefit on a number of Quality of Life measures, such as general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, symptom severity, severity measures and sleep/energy.

Results (pooled data) of four controlled Phase 3 studies with a treatment duration of 12 weeks:

	Placebo	**Solifenacinsuccinate 5 mg o.d.**	**Solifenacin succinate 10 mg o.d.**	**Tolterodine 2 mg b.i.d.**
No. of micturitions/24 h				
Mean baseline	11.9	12.1	11.9	12.1
Mean reduction from baseline	1.4	2.3	2.7	1.9
% change from baseline	(12%)	19%	23%	(16%)
N	1138	552	1158	250
p-value*		<0.001	<0.001	0.004
No. of urgency episodes/24 h				
Mean baseline	6.3	5.9	6.2	5.4
Mean reduction from baseline	2.0	2.9	3.4	2.1
% change from baseline	(32%)	49%	55%	(39%)
N	1124	548	1151	250
p-value*		<0.001	<0.001	0.031
No. of incontinence episodes/24 h				
Mean baseline	2.9	2.6	2.9	2.3
Mean reduction from baseline	1.1	1.5	1.8	1.1
% change from baseline	(38%)	58%	62%	(48%)
N	781	314	778	157
p-value*		<0.001	<0.001	0.009

No. of nocturia episodes/24 h				
Mean baseline	1.8	2	1.8	1.9
Mean reduction from baseline	0.4	0.6	0.6	0.5
% change from baseline	(22%)	30%	33%	(26%)
N	1005	494	1035	232
p-value*		<0.025	<0.001	0.199
Volume voided/micturition				
Mean baseline	166 ml	146 ml	163 ml	147 ml
Mean reduction from baseline	9 ml	32 ml	43 ml	24 ml
% change from baseline	(5%)	21%	26%	(16%)
N	1135	552	1156	250
p-value*		<0.001	<0.001	<0.001
No. of pads/24 h				
Mean baseline	3	2.8	2.7	2.7
Mean reduction from baseline	0. 8	1.3	1.3	1
% change from baseline	(27%)	46%	48%	(37%)
N	238	236	242	250

p-value*		<0.001	<0.001	0.010

Note: In 4 of the pivotal studies, solifenacin succinate 10 mg and placebo were used. In 2 out of the 4 studies also SOLFESIRE 5 mg was used and one of the studies included tolterodine 2 mg bid. Not all parameters and treatment groups were evaluated in each individual study. Therefore, the numbers of patients listed may deviate per parameter and treatment group.

* P-value for the pair wise comparison to placebo.

5.2 Pharmacokinetic properties

Absorption:
After intake of SOLFESIRE tablets, maximum solifenacin plasma concentrations (C_{max}) are reached after 3 to 8 hours. The t_{max} is independent of the dose. The C_{max} and area under the curve (AUC) increase in proportion to the dose between 5 to 40 mg. Absolute bioavailabilityis approximately 90%.

Food intake does not affect the Cmax and AUC of solifenacin.

Distribution:
The apparent volume of distribution of solifenacin following intravenous administration is about 600 L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α1- acid glycoprotein.

Biotransformation:
Solifenacin is extensively metabolised by the liver, primarily by cytochrome P450 3A4 (CYP3A4). However, alternative metabolic pathways exist, that can contribute to the metabolism of solifenacin. The systemic clearance of solifenacin isabout 9.5 L/h and the terminal half life of solifenacin is 45-68 hours. After oral dosing, one pharmacologically active (4R-hydroxy solifenacin) and three inactive metabolites (N-glucuronide, N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been identified in plasma in addition to solifenacin.

Elimination:
After a single administration of 10 mg [14Clabelled] solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance; about 18% as the Noxide metabolite, 9% as the 4RhydroxyNoxide metabolite and 8% as the 4Rhydroxy metabolite (active metabolite).

Linearity/nonlinearity:
Pharmacokinetics are linear in the therapeutic dose range.

Other special populations

Renal impairment:
The AUC and C_{max} of solifenacin in mild and moderate renally impaired patients, was not significantly different from that found in healthy volunteers. In patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) exposure to solifenacin was significantly greater than in the controls with increases in C_{max} of about 30%, AUC of more than 100% and $t_{1/2}$ of more than 60%.

A statistically significant relationship was observed between creatinine clearance and solifenacin clearance.

Pharmacokinetics in patients undergoing haemodialysis has not been studied.

Hepatic impairment:
In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} is not affected, AUC increased with 60% and $t_{1/2}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment has not been studied.

Age:
No dosage adjustment based on patient age is required. The mean rate of absorption expressed as t_{max} was slightly slower in the elderly. C_{max}, AUC and the terminal half-life was approximately 20-25% longer in elderly subjects. These modest differences were considered not clinically significant. The pharmacokinetics of solifenacin has not been established in children and adolescents.

Gender
The pharmacokinetics of solifenacin are not influenced by gender.

Race:
The pharmacokinetics of solifenacin are not influenced by race.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofetal development, genotoxicity, and carcinogenic potential. In the pre-and postnatal development study in mice, solifenacin treatment of the mother during lactation caused dosedependent lower postpartum survival rate, decreased pup weight and slower physical development at clinically relevant levels

6 Pharmaceutical particulars

6.1 List of excipients
Core tablet
Lactose monohydrate
PVP K-30
Talc
Sodium stearyl fumarate

Film coating
Opadry Pink 03F240019 (hypromellose (E464), titanium dioxide (E171), macrogol, talc, yellow iron oxide (E172))

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at room temperature below 30° C.

6.5 Nature and contents of container

PVC/PVDC /Aluminium foil blister, cardboard box, 30 and 90 film tablet.

6.6 Special precautions for disposal and other handling
No special requirements.

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

7 Marketing authorisation holder and Manufacturing Site Addresses

7.1 Marketing Authorization holder
Pharmactive İlaç San. ve Tic. A.Ş
Mahmutbey Mah. Dilmenler Caddesi No:19/3 Bağcılar-İstanbul-TURKEY

7.2 Manufacturer
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8 Marketing authorisation number(s)
TAN 21 HM 0183

9 Date of first authorisation/renewal of the authorisation
29/03/2020

10 Date of revision of the text