Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Darinosin 15 mg Tablets

2. Qualitative and quantitative composition
Each film-coated tablet contains 15 mg of darifenacin (as hydrobromide)

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet
Light peach colored, round, biconvex, bevel edged, film coated tablets, debossed "203" on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications
Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with overactive bladder syndrome.

4.2 Posology and method of administration
Posology

Adults

The recommended starting dose is 7.5 mg daily. After 2 weeks of starting therapy, patients should be reassessed. For those patients requiring greater symptom relief, the dose may be increased to 15 mg daily, based on individual response.

Elderly patients (≥ 65 years)

The recommended starting dose for the elderly is 7.5 mg daily. After 2 weeks of starting therapy, patients should be reassessed for efficacy and safety. For those patients who have an acceptable tolerability profile but require greater symptom relief, the dose may be increased to 15 mg daily, based on individual response (see section 5.2).

Paediatric population

Darifenacin is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

Renal impairment

No dose adjustment is required in patients with impaired renal function. However, caution should be exercised when treating this population (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A). However, there is a risk of increased exposure in this population (see section 5.2).

Patients with moderate hepatic impairment (Child Pugh B) should only be treated if the benefit outweighs the risk, and the dose should be restricted to 7.5 mg daily (see section 5.2). Darifenacin is contraindicated in patients with severe hepatic impairment (Child Pugh C) (see section 4.3).

Patients receiving concomitant treatment with substances that are potent inhibitors of CYP2D6 or moderate inhibitors of CYP3A4

In patients receiving substances that are potent CYP2D6 inhibitors, such as paroxetine, terbinafine, quinidine and cimetidine, treatment should start with the 7.5 mg dose. The dose may be titrated to 15 mg daily to obtain an improved clinical response provided the dose is well tolerated. However, caution should be exercised.

In patients receiving substances that are moderate CYP3A4 inhibitors, such as fluconazole, grapefruit juice and erythromycin, the recommended starting dose is 7.5 mg daily. The dose may be titrated to 15 mg daily to obtain an improved clinical response provided the dose is well tolerated. However, caution should be exercised.

Method of administration

Darifenacin is for oral use. The tablets should be taken once daily with liquid. They can be taken with or without food, and must be swallowed whole and not chewed, divided or crushed.

4.3 Contraindications

Darifenacin is contraindicated in patients with:

- Hypersensitivity to the active substance 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).
- Severe ulcerative colitis.
- Toxic megacolon.
- Concomitant treatment with potent CYP3A4 inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Darifenacin should be administered with caution to patients with autonomic neuropathy, hiatus hernia, clinically significant bladder outflow obstruction, risk for urinary retention, severe constipation or gastrointestinal obstructive disorders, such as pyloric stenosis.

Darifenacin should be used with caution in patients being treated for narrow-angle glaucoma (see section 4.3).

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

Darifenacin should be used with caution in patients with risk of decreased gastrointestinal motility, gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as oral bisphosphonates) that can cause or exacerbate oesophagitis.

Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor over activity.

Caution should be used when prescribing antimuscarinics to patients with pre-existing cardiac diseases.

As with other antimuscarinics, patients should be instructed to discontinue Darifenacin and seek immediate medical attention if they experience oedema of the tongue or laropharynx, or difficulty breathing (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on darifenacin

Darifenacin metabolism is primarily mediated by the cytochrome P450 enzymes CYP2D6 and CYP3A4. Therefore, inhibitors of these enzymes may increase darifenacin exposure.

CYP2D6 inhibitors

In patients receiving substances that are potent CYP2D6 inhibitors (e.g. paroxetine, terbinafine, cimetidine and quinidine) the recommended starting dose should be 7.5 mg daily. The dose may be titrated to 15 mg daily to obtain an improved clinical response provided the dose is well tolerated. Concomitant treatment with potent CYP2D6 inhibitors results in an increase in exposure (e.g. of 33% with 20 mg paroxetine at the 30 mg dose of darifenacin).

CYP3A4 inhibitors

Darifenacin should not be used together with potent CYP3A4 inhibitors (see section 4.3) such as protease inhibitors (e.g. ritonavir), ketoconazole and itraconazole. Potent P-glycoprotein inhibitors such as ciclosporin and verapamil should also be avoided. Co-administration of darifenacin 7.5 mg with the potent CYP3A4 inhibitor ketoconazole 400 mg resulted in a 5-fold increase in steady-state darifenacin AUC. In subjects who are poor metabolisers, darifenacin exposure increased approximately 10-fold. Due to a greater contribution of CYP3A4 after higher darifenacin doses, the magnitude of the effect is expected to be even more pronounced when combining ketoconazole with darifenacin 15 mg.

When co-administered with moderate CYP3A4 inhibitors such as erythromycin, clarithromycin, telithromycin, fluconazole and grapefruit juice, the recommended starting dose of darifenacin should be 7.5 mg daily. The dose may be titrated to 15 mg daily to obtain an improved clinical response provided the dose is well tolerated. Darifenacin AUC_{24} and C_{max} from 30 mg once-daily dosing in subjects who are extensive metabolisers were 95% and 128% higher when erythromycin (moderate CYP3A4 inhibitor) was co-administered with darifenacin than when darifenacin was taken alone.

Enzyme inducers

Substances that are inducers of CYP3A4, such as rifampicin, carbamazepine, barbiturates and St John´s wort (*Hypericum perforatum*) are likely to decrease the plasma concentrations of darifenacin.

Effects of darifenacin on other medicinal products

CYP2D6 substrates

Darifenacin is a moderate inhibitor of the enzyme CYP2D6. Caution should be exercised when darifenacin is used concomitantly with medicinal products that are predominantly metabolised by CYP2D6 and which have a narrow therapeutic window, such as flecainide, thioridazine, or tricyclic antidepressants such as imipramine. The effects of darifenacin on the metabolism of CYP2D6 substrates are mainly clinically relevant for CYP2D6 substrates which are individually dose titrated.

CYP3A4 substrates

Darifenacin treatment resulted in a modest increase in the exposure of the CYP3A4 substrate midazolam. However the data available do not indicate that darifenacin changes either midazolam clearance or bioavailability. It can therefore be concluded that darifenacin administration does not alter the pharmacokinetics of CYP3A4 substrates *in vivo*. The interaction with midazolam lacks clinical relevance, and therefore no dose adjustment is needed for CYP3A4 substrates.

Warfarin

Standard therapeutic prothrombin time monitoring for warfarin should be continued. The effect of warfarin on prothrombin time was not altered when co-administered with darifenacin.

Digoxin

Therapeutic drug monitoring for digoxin should be performed when initiating and ending darifenacin treatment as well as changing the darifenacin dose. Darifenacin 30 mg once daily (two times greater than the recommended daily dose) co-administered with digoxin at steady state resulted in a small increase in digoxin exposure (AUC: 16% and C_{max}: 20%). The increase in digoxin exposure could be caused by competition between darifenacin and digoxin for P-glycoprotein. Other transporter-related interactions cannot be excluded.

Antimuscarinic agents

As with any other antimuscarinic agents, concomitant use of medicinal products that possess antimuscarinic properties, such as oxybutynin, tolterodine and flavoxate, may result in more pronounced therapeutic and side effects. The potentiation of anticholinergic effects with anti-parkinson agents and tricyclic antidepressants may also occur if antimuscarinic agents are used concurrently with such medicinal products. However, no studies involving the interaction with anti-parkinson agents and tricyclic antidepressants have been performed.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are limited amount of data from the use of darifenacin in pregnant women. Studies in animals have shown toxicity to parturition (for details, see section 5.3). Darifenacin is not recommended during pregnancy.

Breast-feeding

Darifenacin is excreted in the milk of rats. It is not known whether darifenacin is excreted in human milk. A risk to the nursing child cannot be excluded. A decision whether to avoid breast-feeding or to abstain from Darifenacin therapy during lactation should be based on a benefit and risk comparison.

Fertility

There are no human fertility data for darifenacin. Darifenacin had no effect on male or female fertility in rats or any effect in the reproductive organs of either sex in rats and dogs (for details, see section 5.3). Women of child bearing potential should be made aware of the lack of fertility data, and Darifenacin should only be given after consideration of individual risks and benefits.

4.7 Effects on ability to drive and use machines.

As with other antimuscarinic agents, Darifenacin may produce effects such as dizziness, blurred vision, insomnia and somnolence. Patients experiencing these side effects should not drive or use machines. For Darifenacin, these side effects have been reported to be uncommon.

4.8 Undesirable effects

Summary of the safety profile

Consistent with the pharmacological profile, the most commonly reported adverse reactions were dry mouth (20.2% and 35% for the 7.5 mg and 15 mg dose, respectively, 18.7% after flexible dose titration, and 8% - 9% for placebo) and constipation (14.8% and 21% for the 7.5 mg and 15 mg dose, respectively, 20.9% after flexible dose titration, and 5.4% - 7.9% for placebo). Anticholinergic effects, in general, are dose-dependent.

However, the patient discontinuation rates due to these adverse reactions were low (dry mouth: 0% - 0.9% and constipation: 0.6% - 2.2% for darifenacin, depending on the dose; and 0% and 0.3% for placebo, for dry mouth and constipation, respectively).

Tabulated list of adverse reactions

The adverse reactions are ranked under heading of frequency using the following 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), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions with Darifenacin 7.5 mg and 15 mg prolonged-release tablets

Infections and infestations	
Uncommon	Urinary tract infection
Psychiatric disorders	
Uncommon	Insomnia, thinking abnormal
Nervous system disorders	
Common	Headache
Uncommon	Dizziness, dysgeusia, somnolence
Eye disorders	
Common	Dry eye
Uncommon	Visual disturbance, including vision blurred
Vascular disorders	
Uncommon	Hypertension
Respiratory, thoracic and mediastinal disorders	
Common	Nasal dryness
Uncommon	Dyspnoea, cough, rhinitis
Gastrointestinal disorders	

Very common	Constipation, dry mouth
Common	Abdominal pain, nausea, dyspepsia
Uncommon	Flatulence, diarrhoea, mouth ulceration
Skin and subcutaneous tissue disorders	
Uncommon	Rash, dry skin, pruritus, hyperhidrosis
Not known	Angioedema
Renal and urinary disorders	
Uncommon	Urinary retention, urinary tract disorder, bladder pain
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, vaginitis
General disorders and administration site conditions	
Uncommon	Oedema peripheral, asthenia, face oedema, oedema
Investigations	
Uncommon	Aspartate aminotransferase increased, alanine aminotransferase increased
Injury, poisoning, and procedural complications	
Uncommon	Injury

Description of selected adverse reactions

In the pivotal clinical trials with doses of Darifenacin 7.5 mg and 15 mg, adverse reactions were reported as presented in the table above. Most of the adverse reactions were of mild or moderate intensity and did not result in discontinuation in the majority of the patients.

Treatment with Darifenacin may possibly mask symptoms associated with gallbladder disease. However, there was no association between the occurrence of adverse events related to the biliary system in darifenacin-treated patients and increasing age.

The incidence of adverse reactions with the doses of Darifenacin 7.5 mg and 15 mg decreased during the treatment period up to 6 months. A similar trend is also seen for the discontinuation rates.

Post-marketing experience

The following events have been reported in association with darifenacin use in worldwide post-marketing experience: generalised hypersensitivity reactions including angioedema, depressed mood/mood alterations, hallucination. Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events cannot be estimated from the available data.

Reporting of suspected adverse reactions:

Healthcare professionals are asked to report any suspected adverse reactions ND PQMPs to https://pv.pharmacyboardkenya.org

4.9 Overdose

Darifenacin has been administered in clinical trials at doses up to 75 mg (five times maximum therapeutic dose). The most common adverse reactions seen were dry mouth, constipation, headache, dyspepsia and nasal dryness. However, overdose with darifenacin can potentially lead to severe anticholinergic effects and should be treated accordingly. Therapy should be aimed at reversing the anticholinergic symptoms under careful medical supervision. The use of agents such as physostigmine can assist in reversing such symptoms.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, drugs for urinary frequency and incontinence; ATC code: G04BD10.

Mechanism of action

Darifenacin is a selective muscarinic M3 receptor antagonist (M_3 SRA) *in vitro*. The M3 receptor is the major subtype that controls urinary bladder muscle contraction. It is not known whether this selectivity for the M3 receptor translates into any clinical advantage when treating symptoms of overactive bladder syndrome.

Clinical efficacy and safety

Cystometric studies performed with darifenacin in patients with involuntary bladder contractions showed increased bladder capacity, increased volume threshold for unstable contractions and diminished frequency of unstable detrusor contractions.

Treatment with Darifenacin administered at dosages of 7.5 mg and 15 mg daily has been investigated in four double-blind, Phase III, randomised, controlled clinical studies in male and female patients with symptoms of overactive bladder. As seen in Table 2 below, a pooled analysis of 3 of the studies for the treatment with both Darifenacin 7.5 mg and 15 mg provided a statistically significant improvement in the primary endpoint, reduction in incontinence episodes, versus placebo.

Table 2: Pooled analysis of data from three Phase III clinical studies assessing fixed doses of 7.5 mg and 15 mg Darifenacin.

Dose	N	Incontinence episodes per week				95% CI	P value[2]
		Baseline (median)	Week 12 (median)	Change from baseline (median)	Differences from placebo[1] (median)		

Darinosin 7.5 mg once daily	335	16.0	4.9	-8.8 (-68%)	-2.0	(-3.6, -0.7)	0.004
Placebo	271	16.6	7.9	-7.0 (-54%)	--	--	--
Darinosin 15 mg once daily	330	16.9	4.1	-10.6 (-77%)	-3.2	(-4.5, -2.0)	<0.001
Placebo	384	16.6	6.4	-7.5 (-58%)	--	--	--

[1] Hodges Lehmann estimate: median difference from placebo in change from baseline

[2] Stratified Wilcoxon test for difference from placebo.

Darifenacin 7.5 mg and 15 mg doses significantly reduced both the severity and number of urinary urgency episodes and the number of micturitions, while significantly increasing the mean volume voided from baseline.

Darifenacin 7.5 mg and 15 mg were associated with statistically significant improvements over placebo in some aspects of quality of life as measured by the Kings Health Questionnaire including incontinence impact, role limitations, social limitations and severity measures.

For both doses of 7.5 mg and 15 mg, the percentage median reduction from baseline in the number of incontinence episodes per week was similar between males and females. The observed differences from placebo for males in terms of percentage and absolute reductions in incontinence episodes was lower than for females.

The effect of treatment with 15 mg and 75 mg of darifenacin on QT/QTc interval was evaluated in a study in 179 healthy adults (44% male: 56% females) aged 18 to 65 for 6 days (to steady state). Therapeutic and supra-therapeutic doses of darifenacin resulted in no increase in QT/QTc interval prolongation from baseline compared to placebo at maximum darifenacin exposure.

5.2 Pharmacokinetic properties

Darifenacin is metabolised by CYP3A4 and CYP2D6. Due to genetic differences, about 7% of the Caucasians lack the CYP2D6 enzyme and are said to be poor metabolisers. A few percent of the population have increased CYP2D6 enzyme levels (ultrafast metabolisers). The information below applies to subjects who have normal CYP2D6 activity (extensive metabolisers) unless otherwise stated.

Absorption

Due to extensive first-pass metabolism darifenacin has a bioavailability of approximately 15% and 19% after 7.5 mg and 15 mg daily doses at steady state. Maximum plasma levels are reached approximately 7 hours after administration of the prolonged-release tablets and steady-state plasma levels are achieved by the sixth day of administration. At steady state, peak-to-trough fluctuations in darifenacin concentrations are small (PTF: 0.87 for 7.5 mg and 0.76 for 15 mg), thereby maintaining therapeutic plasma levels over the dosing interval. Food had no effect on darifenacin pharmacokinetics during multiple-dose administration of prolonged-release tablets.

Distribution

Darifenacin is a lipophilic base and is 98% bound to plasma proteins (primarily to alpha-1-acid-glycoprotein). The steady-state volume of distribution (V_{ss}) is estimated to be 163 litres.

Metabolism

Darifenacin is extensively metabolised by the liver following oral administration.

Darifenacin undergoes significant metabolism by cytochrome CYP3A4 and CYP2D6 in the liver and by CYP3A4 in the gut wall. The three main metabolic routes are as follows:

monohydroxylation in the dihydrobenzofuran ring;

dihydrobenzofuran ring opening and N-dealkylation of the pyrrolidine nitrogen.

The initial products of the hydroxylation and N-dealkylation pathways are major circulating metabolites but none contribute significantly to the overall clinical effect of darifenacin.

The pharmacokinetics of darifenacin at steady state are dose-dependent, due to saturation of the CYP2D6 enzyme.

Doubling the darifenacin dose from 7.5 mg to 15 mg result in a 150% increase in steady-state exposure. This dose-dependency is probably caused by saturation of the CYP2D6 catalysed metabolism possibly together with some saturation of CYP3A4-mediated gut wall metabolism.

Excretion

Following administration of an oral dose of ^{14}C-darifenacin solution to healthy volunteers, approximately 60% of the radioactivity was recovered in the urine and 40% in the faeces. Only a small percentage of the excreted dose was unchanged darifenacin (3%). Estimated darifenacin clearance is 40 litres/hour. The elimination half-life of darifenacin following chronic dosing is approximately 13-19 hours.

Special patient population

Gender

A population pharmacokinetic analysis of patient data indicated that darifenacin exposure was 23% lower in males than females (see section 5.1).

Elderly patients

A population pharmacokinetic analysis of patient data indicated a trend for clearance to decrease with age (19% per decade based on Phase III population pharmacokinetic analysis of patients aged 60–89 years), see section 4.2.

Paediatric patients

The pharmacokinetics of darifenacin have not been established in the paediatric population.

CYP2D6 poor metabolisers

The metabolism of darifenacin in CYP2D6 poor metabolisers is principally mediated by CYP3A4. In one pharmacokinetic study the steady-state exposure in poor metabolisers was 164% and 99% higher during treatment with 7.5 mg and 15 mg once daily, respectively. However, a population pharmacokinetic analyses of Phase III data indicated that on average steady-state exposure is 66% higher in poor metabolisers than in extensive metabolisers. There was considerable overlap between the ranges of exposures seen in these two populations (see section 4.2).

Renal insufficiency

A small study of subjects (n=24) with varying degrees of renal impairment (creatinine clearance between 10 ml/min and 136 ml/min) given darifenacin 15 mg once daily to steady state demonstrated no relationship between renal function and darifenacin clearance (see section 4.2).

Hepatic insufficiency

Darifenacin pharmacokinetics were investigated in subjects with mild (Child Pugh A) or moderate (Child Pugh B) impairment of hepatic function given darifenacin 15 mg once daily to steady state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin. However, protein binding of darifenacin was affected by moderate hepatic impairment. Unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. There were no effects on fertility in male and female rats treated at oral doses up to 50 mg/kg/day (78 times the $AUC_{0\text{-}24h}$ of free plasma concentration at maximum

recommended human dose [MRHD]). There were no effects on reproductive organs in either sex in dogs treated for 1 year at oral doses up to 6 mg/kg/day (82 times the AUC_{0-24h} of free plasma concentration at MRHD). Darifenacin was not teratogenic in rats and rabbits at doses up to 50 and 30 mg/kg/day, respectively. At the dose of 50 mg/kg/day in rats (59 times the AUC_{0-24h} of free plasma concentration at MRHD), delay in the ossification of the sacral and caudal vertebrae was observed. At the dose of 30 mg/kg/day in rabbits (28 times the AUC_{0-24h} of free plasma concentration at MRHD), maternal toxicity and foetotoxicity (increased post implantation loss and decreased number of viable foetuses per litter) were observed. In peri and post-natal studies in rats, dystocia, increased foetal deaths *in utero* and toxicity to post-natal development (pup body weight and development land marks) were observed at systemic exposure levels up to 11 times the AUC_{0-24h} of free plasma concentration at MRHD.

6. Pharmaceutical particulars

6.1 List of excipients

- Purified water
- Magnesium stearate
- Cellulose, microcrystalline PH 112
- Hypromellose (Methocel K4M CR)
- Talc
- Colloidal silicon dioxide
- Titanium Dioxide
- Polyethylene Glycol 400
- Ferric Oxide Red
- Ferric Oxide yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage:

Store below 30℃

Keep the blister packs in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

Alu-PVC/PVDC blister containing 10 tablets

1x10, 3x10, 10x10 Alu-PVC/PVDC blister strips packed in an outer carton.

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

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

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Surgilinks Limited
Surgilinks Building Mombasa Road;
P.O. BOX 14461-00800-Nairobi
Kenya

Manufacturing site address:
Questa Care Ltd
Plot No. 209/7184, Homabay Road Terminus (Gate No: 19), Industrial Area,
P.O. BOX 14461-00800- Nairobi
Kenya

8. Marketing authorization number
CTD9975

9. Date of first registration
03/08/2023

10. Date of revision of the text:
14/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable