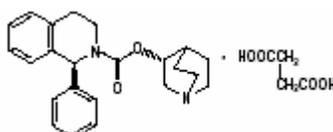


1 **VESicare[®]**
2 **(solifenacin succinate) Tablets**
3
4

5 Revised: January 2008
6

7 **DESCRIPTION**

8 VESicare[®] (solifenacin succinate) is a muscarinic receptor antagonist.
9 Chemically, solifenacin succinate is butanedioic acid, compounded
10 with (1*S*)-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1*H*)-iso-
11 quinolinecarboxylate (1:1) having an empirical formula of C₂₃H₂₆N₂O₂ • C₄H₆O₄,
12 and a molecular weight of 480.55. The structural formula of solifenacin
13 succinate is:
14
15



16
17
18
19 Solifenacin succinate is a white to pale-yellowish-white crystal or crystalline
20 powder. It is freely soluble at room temperature in water, glacial acetic acid,
21 dimethyl sulfoxide, and methanol. Each VESicare tablet contains 5 or 10 mg of
22 solifenacin succinate and is formulated for oral administration. In addition to the
23 active ingredient solifenacin succinate, each VESicare tablet also contains the
24 following inert ingredients: lactose monohydrate, corn starch, hypromellose
25 2910, magnesium stearate, talc, polyethylene glycol 8000 and titanium dioxide
26 with yellow ferric oxide (5 mg VESicare tablet) or red ferric oxide (10 mg
27 VESicare tablet).
28

29 **CLINICAL PHARMACOLOGY**

30 Solifenacin is a competitive muscarinic receptor antagonist. Muscarinic
31 receptors play an important role in several major cholinergically mediated
32 functions, including contractions of urinary bladder smooth muscle and
33 stimulation of salivary secretion.
34

35 **Pharmacokinetics**

36 **Absorption**

37 After oral administration of VESicare to healthy volunteers, peak plasma levels
38 (C_{max}) of solifenacin are reached within 3 to 8 hours after administration, and at
39 steady state ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg VESicare
40 tablets, respectively. The absolute bioavailability of solifenacin is approximately
41 90%, and plasma concentrations of solifenacin are proportional to the dose
42 administered.
43

44 **Effect of food**

45 There is no significant effect of food on the pharmacokinetics of solifenacin.

46

47 **Distribution**

48 Solifenacin is approximately 98% (*in vivo*) bound to human plasma proteins,
49 principally to α_1 -acid glycoprotein. Solifenacin is highly distributed to non-CNS
50 tissues, having a mean steady-state volume of distribution of 600L.

51

52 **Metabolism**

53 Solifenacin is extensively metabolized in the liver. The primary pathway for
54 elimination is by way of CYP3A4; however, alternate metabolic pathways exist.
55 The primary metabolic routes of solifenacin are through N-oxidation of the
56 quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring. One
57 pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low
58 concentrations and unlikely to contribute significantly to clinical activity, and
59 three pharmacologically inactive metabolites (N-glucuronide and the N-oxide
60 and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after
61 oral dosing.

62

63 **Excretion**

64 Following the administration of 10 mg of ^{14}C -solifenacin succinate to healthy
65 volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in
66 the feces over 26 days. Less than 15% (as mean value) of the dose was
67 recovered in the urine as intact solifenacin. The major metabolites identified in
68 urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-
69 oxide of solifenacin and in feces 4R-hydroxy solifenacin. The elimination half-
70 life of solifenacin following chronic dosing is approximately 45-68 hours.

71

72 **Pharmacokinetics in Special Populations**

73 **Age**

74 Multiple dose studies of VESicare in elderly volunteers (65 to 80 years) showed
75 that C_{max} , AUC and $t_{1/2}$ values were 20-25% higher as compared to the younger
76 volunteers (18 to 55 years). (See **PRECAUTIONS, Geriatric Use**).

77

78 **Pediatric**

79 The pharmacokinetics of solifenacin has not been established in pediatric
80 patients.

81

82 **Gender**

83 The pharmacokinetics of solifenacin is not significantly influenced by gender.

84

85 **Race**

86 The number of subjects of different races studied is not adequate to make any
87 conclusions on the effect of race on the pharmacokinetics of solifenacin.

88

89

90 **Renal Impairment**
91 VESicare should be used with caution in patients with renal impairment. There
92 is a 2.1-fold increase in AUC and 1.6-fold increase in $t_{1/2}$ of solifenacin in
93 patients with severe renal impairment. Doses of VESicare greater than 5 mg
94 are not recommended in patients with severe renal impairment ($CL_{cr} < 30$
95 mL/min) (see **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).
96
97 **Hepatic Impairment**
98 VESicare should be used with caution in patients with reduced hepatic function.
99 There is a 2-fold increase in the $t_{1/2}$ and 35% increase in AUC of solifenacin in
100 patients with moderate hepatic impairment. Doses of VESicare greater than 5
101 mg are not recommended in patients with moderate hepatic impairment (Child-
102 Pugh B). VESicare is not recommended for patients with severe hepatic
103 impairment (Child-Pugh C) (see **PRECAUTIONS, DOSAGE AND**
104 **ADMINISTRATION**).
105
106 **Drug-Drug Interactions**
107 **Drugs Metabolized by Cytochrome P450**
108 At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9,
109 2C19, 2D6, or 3A4 derived from human liver microsomes.
110
111 **CYP3A4 Inhibitors**
112 *In vitro* drug metabolism studies have shown that solifenacin is a substrate of
113 CYP3A4. Inducers or inhibitors of CYP3A4 may alter solifenacin
114 pharmacokinetics.
115
116 **Ketoconazole Interaction Study**
117 Following the administration of 10 mg of VESicare in the presence of 400 mg of
118 ketoconazole, a potent inhibitor of CYP3A4, the mean C_{max} and AUC of
119 solifenacin increased by 1.5 and 2.7-fold, respectively. Therefore, it is
120 recommended not to exceed a 5 mg daily dose of VESicare when administered
121 with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors (see
122 **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).
123
124 **Oral Contraceptives**
125 In the presence of solifenacin there are no significant changes in the plasma
126 concentrations of combined oral contraceptives (ethinyl estradiol/levogestrel).
127
128 **Warfarin**
129 Solifenacin has no significant effect on the pharmacokinetics of *R*-warfarin or *S*-
130 warfarin.
131
132 **Digoxin**
133 Solifenacin had no significant effect on the pharmacokinetics of digoxin (0.125
134 mg/day) in healthy subjects.
135

136 **Cardiac Electrophysiology**

137 The effect of 10 mg and 30 mg solifenacin succinate on the QT interval was
138 evaluated at the time of peak plasma concentration of solifenacin in a multi-
139 dose, randomized, double-blind, placebo and positive-controlled (moxifloxacin
140 400 mg) trial. Subjects were randomized to one of two treatment groups after
141 receiving placebo and moxifloxacin sequentially. One group (n=51) went on to
142 complete 3 additional sequential periods of dosing with solifenacin 10, 20, and
143 30 mg while the second group (n=25) in parallel completed a sequence of
144 placebo and moxifloxacin. Study subjects were female volunteers aged 19 to
145 79 years. The 30 mg dose of solifenacin succinate (three times the highest
146 recommended dose) was chosen for use in this study because this dose results
147 in a solifenacin exposure that covers those observed upon co-administration of
148 10 mg VESicare with potent CYP3A4 inhibitors (e.g. ketoconazole, 400 mg).
149 Due to the sequential dose escalating nature of the study, baseline EKG
150 measurements were separated from the final QT assessment (of the 30 mg
151 dose level) by 33 days.

152
153 The median difference from baseline in heart rate associated with the 10 and 30
154 mg doses of solifenacin succinate compared to placebo was -2 and 0
155 beats/minute, respectively. Because a significant period effect on QTc was
156 observed, the QTc effects were analyzed utilizing the parallel placebo control
157 arm rather than the pre-specified intra-patient analysis. Representative results
158 are shown in Table 1.

159
160 **Table 1. QTc changes in msec (90%CI) from baseline at T_{max} (relative to placebo)***

| Drug/Dose | Fridericia method (using mean difference) |
|-------------------|----------------------------------------------|
| Solifenacin 10 mg | 2 (-3,6) |
| Solifenacin 30 mg | 8 (4,13) |

161 *Results displayed are those derived from the parallel design portion of the study and represent
162 the comparison of Group 1 to time-matched placebo effects in Group 2

163
164 Moxifloxacin was included as a positive control in this study and, given the
165 length of the study, its effect on the QT interval was evaluated in 3 different
166 sessions. The placebo subtracted mean changes (90% CI) in QTcF for
167 moxifloxacin in the three sessions were 11 (7, 14), 12 (8, 17), and 16 (12, 21),
168 respectively.

169
170 The QT interval prolonging effect appeared greater for the 30 mg compared to
171 the 10 mg dose of solifenacin. Although the effect of the highest solifenacin
172 dose (three times the maximum therapeutic dose) studied did not appear as
173 large as that of the positive control moxifloxacin at its therapeutic dose, the
174 confidence intervals overlapped. This study was not designed to draw direct
175 statistical conclusions between the drugs or the dose levels.

176
177
178

179 **CLINICAL STUDIES**

180 VESIcare was evaluated in four twelve-week, double-blind, randomized,
 181 placebo-controlled, parallel group, multicenter clinical trials for the treatment of
 182 overactive bladder in patients having symptoms of urinary frequency, urgency,
 183 and/or urge or mixed incontinence (with a predominance of urge). Entry criteria
 184 required that patients have symptoms of overactive bladder for ≥ 3 months
 185 duration. These studies involved 3027 patients (1811 on VESIcare and 1216
 186 on placebo), and approximately 90% of these patients completed the 12-week
 187 studies. Two of the four studies evaluated the 5 and 10 mg VESIcare doses
 188 and the other two evaluated only the 10 mg dose. All patients completing the
 189 12-week studies were eligible to enter an open label, long term extension study
 190 and 81% of patients enrolling completed the additional 40-week treatment
 191 period. The majority of patients were Caucasian (93%) and female (80%) with
 192 a mean age of 58 years.

193

194 The primary endpoint in all four trials was the mean change from baseline to 12
 195 weeks in number of micturitions/24 hours. Secondary endpoints included mean
 196 change from baseline to 12 weeks in number of incontinence episodes/24 hours,
 197 and mean volume voided per micturition. The efficacy of VESIcare was similar
 198 across patient age and gender. The mean reduction in the number of
 199 micturitions per 24 hours was significantly greater with VESIcare 5 mg (2.3;
 200 $p < 0.001$) and VESIcare 10 mg (2.7; $p < 0.001$) compared to placebo, (1.4).

201

202 The mean reduction in the number of incontinence episodes per 24 hours was
 203 significantly greater with VESIcare 5 mg (1.5; $p < 0.001$) and VESIcare 10 mg
 204 (1.8; $p < 0.001$) treatment groups compared to placebo (1.1). The mean
 205 increase in the volume voided per micturition was significantly greater with
 206 VESIcare 5 mg (32.3 mL; $p < 0.001$) and VESIcare 10 mg (42.5 mL; $p < 0.001$)
 207 compared with placebo (8.5 mL).

208

209 The results for the primary and secondary endpoints in the four individual 12-
 210 week clinical studies of VESIcare are reported in Tables 2 through 5.

211

212 **Table 2. Mean Change from Baseline to Endpoint for VESIcare (5 mg and 10 mg daily)**
 213 **and Placebo: 905-CL-015**

| Parameter | Placebo (N=253) Mean (SE) | VESIcare 5 mg (N=266) Mean (SE) | VESIcare 10 mg (N=264) Mean (SE) |
|------------------------------------------------------|---------------------------------|------------------------------------------|-------------------------------------------|
| Urinary Frequency (Number of Micturitions/24 hours)* | | | |
| Baseline | 12.2 (0.26) | 12.1 (0.24) | 12.3 (0.24) |
| Reduction | 1.2 (0.21) | 2.2 (0.18) | 2.6 (0.20) |
| P value vs. placebo | | <0.001 | <0.001 |
| Number of Incontinence Episodes/24 hours** | | | |
| Baseline | 2.7 (0.23) | 2.6 (0.22) | 2.6 (0.23) |
| Reduction | 0.8 (0.18) | 1.4 (0.15) | 1.5 (0.18) |
| P value vs. placebo | | <0.01 | <0.01 |

| | | | |
|--------------------------------------|--------------|--------------|--------------|
| Volume Voided per micturition [mL]** | | | |
| Baseline | 143.8 (3.37) | 149.6 (3.35) | 147.2 (3.15) |
| Increase | 7.4 (2.28) | 32.9 (2.92) | 39.2 (3.11) |
| P value vs. placebo | | <0.001 | <0.001 |

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* Primary endpoint
** Secondary endpoint

Table 3. Mean Change from Baseline to Endpoint for VESicare (5 mg and 10 mg daily) and Placebo: 905-CL-018

| Parameter | Placebo (N=281) | VESicare 5 mg (N=286) | VESicare 10 mg (N=290) |
|------------------------------------------------------|--------------------|-----------------------------|------------------------------|
| | Mean (SE) | Mean (SE) | Mean (SE) |
| Urinary Frequency (Number of Micturitions/24 hours)* | | | |
| Baseline | 12.3 (0.23) | 12.1 (0.23) | 12.1 (0.21) |
| Reduction | 1.7 (0.19) | 2.4 (0.17) | 2.9 (0.18) |
| P value vs. placebo | | <0.001 | <0.001 |
| Number of Incontinence Episodes/24 hours** | | | |
| Baseline | 3.2 (0.24) | 2.6 (0.18) | 2.8 (0.20) |
| Reduction | 1.3 (0.19) | 1.6 (0.16) | 1.6 (0.18) |
| P value vs. placebo | | <0.01 | 0.016 |
| Volume Voided per micturition [mL]** | | | |
| Baseline | 147.2 (3.18) | 148.5 (3.16) | 145.9 (3.42) |
| Increase | 11.3 (2.52) | 31.8 (2.94) | 36.6 (3.04) |
| P value vs. placebo | | <0.001 | <0.001 |

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* Primary endpoint
** Secondary endpoint

Table 4. Mean Change from Baseline to Endpoint for VESicare (10 mg daily) and Placebo: 905-CL-013

| Parameter | Placebo (N=309) | VESicare 10 mg (N=306) |
|------------------------------------------------------|--------------------|------------------------------|
| | Mean (SE) | Mean (SE) |
| Urinary Frequency (Number of Micturitions/24 hours)* | | |
| Baseline | 11.5 (0.18) | 11.7 (0.18) |
| Reduction | 1.5 (0.15) | 3.0 (0.15) |
| P value vs. placebo | | <0.001 |
| Number of Incontinence Episodes/24 hours** | | |
| Baseline | 3.0 (0.20) | 3.1 (0.22) |
| Reduction | 1.1 (0.16) | 2.0 (0.19) |
| P value vs. placebo | | <0.001 |
| Volume Voided per micturition [mL]** | | |
| Baseline | 190.3 (5.48) | 183.5 (4.97) |
| Increase | 2.7 (3.15) | 47.2 (3.79) |
| P value vs. placebo | | <0.001 |

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* Primary endpoint
** Secondary endpoint

231
232
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Table 5. Mean Change from Baseline to Endpoint for VESicare (10 mg daily) and Placebo: 905-CL-014

| Parameter | Placebo (N=295) Mean (SE) | VESicare 10 mg (N=298) Mean (SE) |
|------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------|
| Urinary Frequency (Number of Micturitions/24 hours)* Baseline Reduction P value vs. placebo | 11.8 (0.18) 1.3 (0.16) | 11.5 (0.18) 2.4 (0.15) <0.001 |
| Number of Incontinence Episodes/24 hours** Baseline Reduction P value vs. placebo | 2.9 (0.18) 1.2 (0.15) | 2.9 (0.17) 2.0 (0.15) <0.001 |
| Volume Voided per micturition [mL]** Baseline Increase P value vs. placebo | 175.7 (4.44) 13.0 (3.45) | 174.1 (4.15) 46.4 (3.73) <0.001 |

234
235
236

* Primary endpoint

** Secondary endpoint

237

INDICATIONS AND USAGE

238
239
240

VESicare is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

241

CONTRAINDICATIONS

242
243
244
245

VESicare is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

246

PRECAUTIONS

247

Bladder Outflow Obstruction

248
249
250
251

VESicare, like other anticholinergic drugs, should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

252

Gastrointestinal Obstructive Disorders and Decreased GI Motility

253
254
255

VESicare, like other anticholinergics, should be used with caution in patients with decreased gastrointestinal motility.

256

Controlled Narrow-Angle Glaucoma

257
258
259

VESicare should be used with caution in patients being treated for narrow-angle glaucoma. (See **CONTRAINDICATIONS**)

260

Reduced Renal Function

261
262
263
264

VESicare should be used with caution in patients with reduced renal function. Doses of VESicare greater than 5 mg are not recommended in patients with severe renal impairment ($CL_{cr} < 30$ mL/min). (See **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**)

265

266 **Reduced Hepatic Function**

267 VESicare should be used with caution in patients with reduced hepatic function.
268 Doses of VESicare greater than 5 mg are not recommended in patients with
269 moderate hepatic impairment (Child-Pugh B). VESicare is not recommended
270 for patients with severe hepatic impairment (Child-Pugh C). (See **CLINICAL**
271 **PHARMACOLOGY, DOSAGE AND ADMINISTRATION**)

272

273 **Drug-Drug Interactions**

274 Do not exceed a 5 mg daily dose of VESicare when administered with
275 therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors. (See
276 **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**)

277

278 **Patients with Congenital or Acquired QT Prolongation**

279 In a study of the effect of solifenacin on the QT interval in 76 healthy women
280 (See **CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**), the QT
281 prolonging effect appeared less with solifenacin 10 mg than with 30 mg (three
282 times the maximum recommended dose), and the effect of solifenacin 30 mg
283 did not appear as large as that of the positive control moxifloxacin at its
284 therapeutic dose. This observation should be considered in clinical decisions to
285 prescribe VESicare for patients with a known history of QT prolongation or
286 patients who are taking medications known to prolong the QT interval.

287

288 **Information for Patients**

289 Patients should be informed that antimuscarinic agents such as VESicare have
290 been associated with constipation and blurred vision. Patients should be
291 advised to contact their physician if they experience severe abdominal pain or
292 become constipated for 3 or more days. Because VESicare may cause blurred
293 vision, patients should be advised to exercise caution in decisions to engage in
294 potentially dangerous activities until the drug's effect on the patient's vision has
295 been determined. Heat prostration (due to decreased sweating) can occur
296 when anticholinergic drugs, such as VESicare, are used in a hot environment.
297 Patients should read the patient leaflet entitled "Patient Information VESicare"
298 before starting therapy with VESicare.

299

300 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

301 Solifenacin succinate was not mutagenic in the *in vitro* *Salmonella typhimurium*
302 or *Escherichia coli* microbial mutagenicity test or chromosomal aberration test in
303 human peripheral blood lymphocytes with or without metabolic activation, or in
304 the *in vivo* micronucleus test in rats.

305

306 No increase in tumors was found following the administration of solifenacin
307 succinate to male and female mice for 104 weeks at doses up to 200 mg/kg/day
308 (5 and 9 times human exposure at the maximum recommended human dose
309 [MRHD], respectively), and male and female rats for 104 weeks at doses up to
310 20 and 15 mg/kg/day, respectively (<1 times exposure at the MRHD).

311
312 Solifenacin succinate had no effect on reproductive function, fertility or early
313 embryonic development of the fetus in male and female mice treated with 250
314 mg/kg/day (13 times exposure at the MRHD) of solifenacin succinate, and in
315 male rats treated with 50 mg/kg/day (<1 times exposure at the MRHD) and
316 female rats treated with 100 mg/kg/day (1.7 times exposure at the MRHD) of
317 solifenacin succinate.

318

319 **Pregnancy, Teratogenic Effects, Pregnancy Category**

320 ***Pregnancy Category C***

321 Reproduction studies have been performed in mice, rats and rabbits. After oral
322 administration of ¹⁴C-solifenacin succinate to pregnant mice, drug-related
323 material was shown to cross the placental barrier. No embryotoxicity or
324 teratogenicity was observed in mice treated with 30 mg/kg/day (1.2 times
325 exposure at the maximum recommended human dose [MRHD]). Administration
326 of solifenacin succinate to pregnant mice at doses of 100 mg/kg and greater
327 (3.6 times exposure at the MRHD), during the major period of organ
328 development resulted in reduced fetal body weights. Administration of 250
329 mg/kg (7.9 times exposure at the MRHD) to pregnant mice resulted in an
330 increased incidence of cleft palate. In utero and lactational exposures to
331 maternal doses of solifenacin succinate of 100 mg/kg/day and greater (3.6
332 times exposure at the MRHD) resulted in reduced peripartum and postnatal
333 survival, reductions in body weight gain, and delayed physical development
334 (eye opening and vaginal patency). An increase in the percentage of male
335 offspring was also observed in litters from offspring exposed to maternal doses
336 of 250 mg/kg/day. No embryotoxic effects were observed in rats at up to 50
337 mg/kg/day (<1 times exposure at the MRHD) or in rabbits at up to 50 mg/kg/day
338 (1.8 times exposure at the MRHD). There are no adequate and well-controlled
339 studies in pregnant women. Because animal reproduction studies are not
340 always predictive of human response, VESicare should be used during
341 pregnancy only if the potential benefit justifies the potential risk to the fetus.

342

343 **Labor and Delivery**

344 The effect of VESicare on labor and delivery in humans has not been studied.

345

346 There were no effects on natural delivery in mice treated with 30 mg/kg/day (1.2
347 times exposure at the maximum recommended human dose [MRHD]).
348 Administration of solifenacin succinate at 100 mg/kg/day (3.6 times exposure at
349 the MRHD) or greater increased peripartum pup mortality.

350

351 **Nursing Mothers**

352 After oral administration of ¹⁴C-solifenacin succinate to lactating mice,
353 radioactivity was detected in maternal milk. There were no adverse
354 observations in mice treated with 30 mg/kg/day (1.2 times exposure at the
355 maximum recommended human dose [MRHD]). Pups of female mice treated
356 with 100 mg/kg/day (3.6 times exposure at the MRHD) or greater revealed

357 reduced body weights, postpartum pup mortality or delays in the onset of reflex
358 and physical development during the lactation period.

359
360 It is not known whether solifenacin is excreted in human milk. Because many
361 drugs are excreted in human milk, VESlcare should not be administered during
362 nursing. A decision should be made whether to discontinue nursing or to
363 discontinue VESlcare in nursing mothers.

364
365 **Pediatric Use**

366 The safety and effectiveness of VESlcare in pediatric patients have not been
367 established.

368
369 **Geriatric Use**

370 In placebo controlled clinical studies, similar safety and effectiveness were
371 observed between older (623 patients \geq 65 years and 189 patients \geq 75 years)
372 and younger patients (1188 patients $<$ 65 years) treated with VESlcare (See
373 **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations**).

374
375 **ADVERSE REACTIONS**

376 VESlcare has been evaluated for safety in 1811 patients in randomized,
377 placebo-controlled trials. Expected side effects of antimuscarinic agents are dry
378 mouth, constipation, blurred vision (accommodation abnormalities), urinary
379 retention, and dry eyes. The most common adverse events reported in patients
380 treated with VESlcare were dry mouth and constipation and the incidence of
381 these side effects was higher in the 10 mg compared to the 5 mg dose group.
382 In the four 12-week double-blind clinical trials there were three intestinal serious
383 adverse events in patients, all treated with VESlcare 10 mg (one fecal
384 impaction, one colonic obstruction, and one intestinal obstruction). The overall
385 rate of serious adverse events in the double-blind trials was 2%. Angioneurotic
386 edema has been reported in one patient taking VESlcare 5 mg. Compared to
387 twelve weeks of treatment with VESlcare, the incidence and severity of adverse
388 events were similar in patients who remained on drug for up to 12 months. The
389 most frequent reason for discontinuation due to an adverse event was dry
390 mouth, 1.5%. Table 6 lists adverse events, regardless of causality, that were
391 reported in randomized, placebo-controlled trials at an incidence greater than
392 placebo and in 1% or more of patients treated with VESlcare 5 or 10 mg once
393 daily for up to 12 weeks.

394
395 **Table 6. Percentages of Patients with Treatment-emergent Adverse Events Exceeding**
396 **Placebo Rate and Reported by 1% or More Patients for Combined Pivotal Studies**

| SYSTEM ORGAN CLASS MedDRA Preferred Term | Placebo (%) | VESlcare 5 mg (%) | VESlcare 10 mg (%) |
|-----------------------------------------------------|------------------------|----------------------------------|-----------------------------------|
| Number of Patients | 1216 | 578 | 1233 |
| Number of Patients with Treatment-emergent AE | 634 | 265 | 773 |
| GASTROINTESTINAL DISORDERS | | | |

| | | | |
|------------------------------------------------------|-----|------|------|
| Dry Mouth | 4.2 | 10.9 | 27.6 |
| Constipation | 2.9 | 5.4 | 13.4 |
| Nausea | 2.0 | 1.7 | 3.3 |
| Dyspepsia | 1.0 | 1.4 | 3.9 |
| Abdominal Pain Upper | 1.0 | 1.9 | 1.2 |
| Vomiting NOS | 0.9 | 0.2 | 1.1 |
| INFECTIONS AND INFESTATIONS | | | |
| Urinary Tract Infection NOS | 2.8 | 2.8 | 4.8 |
| Influenza | 1.3 | 2.2 | 0.9 |
| Pharyngitis NOS | 1.0 | 0.3 | 1.1 |
| NERVOUS SYSTEM DISORDERS | | | |
| Dizziness | 1.8 | 1.9 | 1.8 |
| EYE DISORDERS | | | |
| Vision Blurred | 1.8 | 3.8 | 4.8 |
| Dry Eyes NOS | 0.6 | 0.3 | 1.6 |
| RENAL AND URINARY DISORDERS | | | |
| Urinary Retention | 0.6 | 0 | 1.4 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| Edema Lower Limb | 0.7 | 0.3 | 1.1 |
| Fatigue | 1.1 | 1.0 | 2.1 |
| PSYCHIATRIC DISORDERS | | | |
| Depression NOS | 0.8 | 1.2 | 0.8 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| Cough | 0.2 | 0.2 | 1.1 |
| VASCULAR DISORDERS | | | |
| Hypertension NOS | 0.6 | 1.4 | 0.5 |

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Post-Marketing Surveillance

The following events have been reported in association with solifenacin use in worldwide postmarketing experience: *General*: hypersensitivity reactions, including angioedema, rash, pruritis, and urticaria; *Central Nervous*: confusion and hallucinations; *Cardiovascular*: QT prolongation; Torsade de Pointes. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of solifenacin in their causation cannot be reliably determined.

409

410 **OVERDOSAGE**

411 **Acute**

412 Overdosage with VESicare can potentially result in severe anticholinergic
413 effects and should be treated accordingly. The highest VESicare dose given to
414 human volunteers was a single 100 mg dose.

415

416 **Chronic**

417 Intolerable anticholinergic side effects (fixed and dilated pupils, blurred vision,
418 failure of heel-to-toe exam, tremors and dry skin) occurred on day 3 in normal
419 volunteers taking 50 mg daily (5 times the maximum recommended therapeutic
420 dose) and resolved within 7 days following discontinuation of drug.

421

422 **Treatment of Overdosage**

423 In the event of overdose with VESicare, treat with gastric lavage and
424 appropriate supportive measures. ECG monitoring is also recommended.

425

426 **DOSAGE AND ADMINISTRATION**

427 The recommended dose of VESicare is 5 mg once daily. If the 5 mg dose is
428 well tolerated, the dose may be increased to 10 mg once daily.

429

430 VESicare should be taken with liquids and swallowed whole. VESicare can be
431 administered with or without food.

432

433 **Dose Adjustment in Renal Impairment**

434 For patients with severe renal impairment ($CL_{cr} < 30$ mL/min), a daily dose of
435 VESicare greater than 5 mg is not recommended.

436

437 **Dose Adjustment in Hepatic Impairment**

438 For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of
439 VESicare greater than 5 mg is not recommended. Use of VESicare in patients
440 with severe hepatic impairment (Child-Pugh C) is not recommended.

441

442 **Dose Adjustment CYP3A4 Inhibitors**

443 When administered with therapeutic doses of ketoconazole or other potent
444 CYP3A4 inhibitors, a daily dose of VESicare greater than 5 mg is not
445 recommended.

446

447 **HOW SUPPLIED**

448 VESicare is supplied as round, film-coated tablets, available in bottles and unit
449 dose blister packages as follows:

450

451

452

453

**strength
color
debossed**

**5 mg
light yellow
logo, 150**

**10 mg
light pink
logo, 151**

Bottle of 30
Bottle of 90
Unit Dose Pack of 100

NDC 51248-150-01
NDC 51248-150-03
NDC 51248-150-52

NDC 51248-151-01
NDC 51248-151-03
NDC 51248-151-52

454

455 Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F -86°F)
456 [see USP Controlled Room Temperature]

457

458 **Rx Only**

459

460 **Manufactured by:**

461 Astellas Pharma Technologies Inc.
462 Norman, Oklahoma 73072

463

464 **Marketed by:**

465 Astellas Pharma US, Inc.
466 Deerfield, Illinois 60015-2548

467

468 **Marketed and Distributed by:**

469 GlaxoSmithKline
470 Research Triangle Park
471 North Carolina 27709

472

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475

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