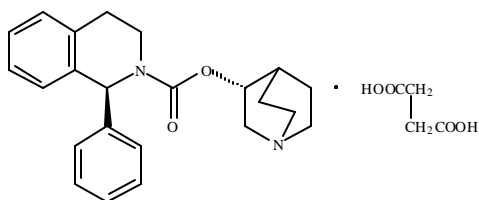


1 **VESicare[®] – Solifenacin Succinate**

2

3 **DESCRIPTION**

4 VESicare[®] (solifenacin succinate) is a muscarinic receptor antagonist. Chemically, solifenacin
5 succinate is butanedioic acid, compounded with (1*S*)-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl 3,4-
6 dihydro-1-phenyl-2(1*H*)-isoquinolinecarboxylate (1:1) having an empirical formula of
7 C₂₃H₂₆N₂O₂·C₄H₆O₄, and a molecular weight of 480.55. The structural formula of solifenacin
8 succinate is:



9

10 Solifenacin succinate is a white to pale-yellowish-white crystal or crystalline powder. It is freely
11 soluble at room temperature in water, glacial acetic acid, dimethyl sulfoxide, and methanol. Each
12 VESicare tablet contains 5 or 10 mg of solifenacin succinate and is formulated for oral
13 administration. In addition to the active ingredient solifenacin succinate, each VESicare tablet
14 also contains the following inert ingredients: lactose monohydrate, corn starch, hypromellose
15 2910, magnesium stearate, talc, polyethylene glycol 8000 and titanium dioxide with yellow ferric
16 oxide (5 mg VESicare tablet) or red ferric oxide (10 mg VESicare tablet).

17

18 **CLINICAL PHARMACOLOGY**

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

22

23 **Pharmacokinetics**

24 **Absorption:** After oral administration of VESicare to healthy volunteers, peak plasma levels
25 (C_{max}) of solifenacin are reached within 3 to 8 hours after administration, and at steady state
26 ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg VESicare tablets, respectively. The absolute
27 bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are
28 proportional to the dose administered.

29

29 **Effect of food:** There is no significant effect of food on the pharmacokinetics of solifenacin.

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

33 **Metabolism:** Solifenacin is extensively metabolized in the liver. The primary pathway for
34 elimination is by way of CYP3A4; however, alternate metabolic pathways exist. The primary
35 metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-
36 hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-
37 hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to
38 clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-
39 oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral
40 dosing.

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

47 **Pharmacokinetics in special populations**

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

51 **Pediatric:** The pharmacokinetics of solifenacin have not been established in pediatric patients.

52 **Gender:** The pharmacokinetics of solifenacin are not significantly influenced by gender.

53 **Race:** The number of subjects of different races studied is not adequate to make any conclusions
54 on the effect of race on the pharmacokinetics of solifenacin.

55 **Renal Impairment:** VESicare should be used with caution in patients with renal impairment.
56 There is a 2.1-fold increase in AUC and 1.6-fold increase in $t_{1/2}$ of solifenacin in patients with
57 severe renal impairment. Doses of VESicare greater than 5 mg are not recommended in patients
58 with severe renal impairment ($\text{CL}_{\text{cr}} < 30 \text{ mL/min}$) (See PRECAUTIONS, DOSAGE AND
59 ADMINISTRATION).

60

60 **Hepatic Impairment:** VESicare should be used with caution in patients with reduced hepatic
61 function. There is a 2-fold increase in the $t_{1/2}$ and 35% increase in AUC of solifenacin in patients
62 with moderate hepatic impairment. Doses of VESicare greater than 5 mg are not recommended
63 in patients with moderate hepatic impairment (Child-Pugh B). VESicare is not recommended for
64 patients with severe hepatic impairment (Child-Pugh C) (See PRECAUTIONS, DOSAGE AND
65 ADMINISTRATION).

66

67 **Drug-Drug Interactions**

68 **Drugs Metabolized by Cytochrome P450:** At therapeutic concentrations, solifenacin does not
69 inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes.

70 **CYP 3A4 Inhibitors:** In vitro drug metabolism studies have shown that solifenacin is a substrate
71 of CYP3A4. Inducers or inhibitors of CYP3A4 may alter solifenacin pharmacokinetics.

72 **Ketoconazole Interaction Study:** Following the administration of 10 mg of VESicare in the
73 presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean C_{max} and AUC of
74 solifenacin increased by 1.5 and 2.7-fold, respectively. Therefore, it is recommended not to
75 exceed a 5 mg daily dose of VESicare when administered with therapeutic doses of ketoconazole
76 or other potent CYP3A4 inhibitors (See PRECAUTIONS, DOSAGE AND
77 ADMINISTRATION).

78 **Oral Contraceptives:** In the presence of solifenacin there are no significant changes in the
79 plasma concentrations of combined oral contraceptives (ethinyl estradiol/levogestrel).

80 **Warfarin:** Solifenacin has no significant effect on the pharmacokinetics of *R*-warfarin or *S*-
81 warfarin.

82 **Digoxin:** Solifenacin had no significant effect on the pharmacokinetics of digoxin (0.125
83 mg/day) in healthy subjects.

84

85 **Cardiac Electrophysiology**

86 The effect of 10 mg and 30 mg solifenacin succinate on the QT interval was evaluated at the time
87 of peak plasma concentration of solifenacin in a multi-dose, randomized, double-blind, placebo
88 and positive-controlled (moxifloxacin 400 mg) trial. Subjects were randomized to one of two
89 treatment groups after receiving placebo and moxifloxacin sequentially. One group (n=51) went
90 on to complete 3 additional sequential periods of dosing with solifenacin 10, 20, and 30 mg,
91 while the second group (n= 25) in parallel completed a sequence of placebo and moxifloxacin.
92 Study subjects were female volunteers aged 19 to 79 years. The 30 mg dose of solifenacin
93 succinate (three times the highest recommended dose) was chosen for use in this study because

94 this dose results in a solifenacin exposure that covers those observed upon co-administration of
95 10 mg VESicare with potent CYP 3A4 inhibitors (e.g. ketoconazole, 400 mg). Due to the
96 sequential dose escalating nature of the study, baseline EKG measurements were separated from
97 the final QT assessment (of the 30 mg dose level) by 33 days.

98

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

104

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

105

106

107

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

108 Moxifloxacin was included as a positive control in this study and, given the length of the study,
109 its effect on the QT interval was evaluated in 3 different sessions. The placebo subtracted mean
110 changes (90% CI) in QTcF for moxifloxacin in the three sessions were 11 (7, 14), 12 (8, 17), and
111 16 (12, 21), respectively.

112

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

118

119 **CLINICAL STUDIES**

120 VESicare was evaluated in four twelve-week, double-blind, randomized, placebo-controlled,
121 parallel group, multicenter clinical trials for the treatment of overactive bladder in patients having
122 symptoms of urinary frequency, urgency and/or urge or mixed incontinence (with a
123 predominance of urge). Entry criteria required that patients have symptoms of overactive bladder

124 for ≥ 3 months duration. These studies involved 3027 patients (1811 on VESicare and 1216 on
125 placebo), and approximately 90% of these patients completed the 12-week studies. Two of the
126 four studies evaluated the 5 and 10 mg VESicare doses and the other two evaluated only the 10
127 mg dose. All patients completing the 12-week studies were eligible to enter an open label, long
128 term extension study and 81% of patients enrolling completed the additional 40-week treatment
129 period. The majority of patients were Caucasian (93%) and female (80%) with a mean age of 58
130 years.

131 The primary endpoint in all four trials was the mean change from baseline to 12 weeks in number
132 of micturitions/24 hours. Secondary endpoints included mean change from baseline to 12 weeks
133 in number of incontinence episodes/24 hours, and mean volume voided per micturition. The
134 efficacy of VESicare was similar across patient age and gender. The mean reduction in the
135 number of micturitions per 24 hours was significantly greater with VESicare 5 mg (2.3; $p<0.001$)
136 and VESicare 10 mg (2.7; $p<0.001$) compared to placebo, (1.4).

137 The mean reduction in the number of incontinence episodes per 24 hours was significantly greater
138 with VESicare 5 mg (1.5; $p<0.001$) and VESicare 10 mg (1.8; $p<0.001$) treatment groups
139 compared to placebo (1.1). The mean increase in the volume voided per micturition was
140 significantly greater with VESicare 5 mg (32.3 mL; $p<0.001$) and VESicare 10 mg (42.5 mL;
141 $p<0.001$) compared with placebo (8.5 mL).

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

144

145

145 **Table 2. Mean Change from Baseline to Endpoint for VESicare (5mg and**
 146 **10mg daily) and Placebo: 905-CL-015**
 147

| Parameter | Placebo (N=253) Mean (SE) | VESicare 5mg (N=266) Mean (SE) | VESicare 10mg (N=264) Mean (SE) |
|---|---------------------------------|--------------------------------------|---------------------------------------|
| Urinary Frequency (Number of Micturitions / 24hours)* | | | |
| 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 |

148 *Primary endpoint
 149 **Secondary endpoint

150
 151 **Table 3. Mean Change from Baseline to Endpoint for VESicare (5mg and**
 152 **10mg daily) and Placebo: 905-CL-018**
 153

| Parameter | Placebo (N=281) Mean (SE) | VESicare 5mg (N=286) Mean (SE) | VESicare 10mg (N=290) Mean (SE) |
|---|---------------------------------|--------------------------------------|---------------------------------------|
| Urinary Frequency (Number of Micturitions / 24hours)* | | | |
| 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 |

154 *Primary endpoint
 155 **Secondary endpoint

156 **Table 4. Mean Change from Baseline to Endpoint for VESicare (10mg daily)**
 157 **and Placebo: 905-CL-013**
 158

| Parameter | Placebo (N=309) Mean (SE) | VESicare 10mg (N=306) Mean (SE) |
|---|---------------------------------|---------------------------------------|
| Urinary Frequency (Number of Micturitions / 24hours)* | | |
| 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 |

*Primary endpoint
 **Secondary endpoint

159
 160
 161

162 **Table 5. Mean Change from Baseline to Endpoint for VESicare (10mg daily)**
 163 **and Placebo: 905-CL-014**
 164

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

*Primary endpoint
 **Secondary endpoint

165
 166
 167
 168

168 **INDICATIONS AND USAGE**

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

171

172 **CONTRAINDICATIONS**

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

176

177 **PRECAUTIONS**

178 **Bladder Outflow Obstruction**

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

181 **Gastrointestinal Obstructive Disorders and Decreased GI Motility**

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

184 **Controlled Narrow-Angle Glaucoma**

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

187 **Reduced Renal Function**

188 VESicare should be used with caution in patients with reduced renal function. Doses of
189 VESicare greater than 5 mg are not recommended in patients with severe renal impairment (CL_{cr}
190 < 30 mL/min). (See CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION)

191 **Reduced Hepatic Function**

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

196 **Drug-Drug Interaction**

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

200

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

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

208

209 **Information for Patients**

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

218

219 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

223

224 No increase in tumors was found following the administration of solifenacin succinate to male
225 and female mice for 104 weeks at doses up to 200 mg/kg/day (5 and 9 times human exposure at
226 the maximum recommended human dose [MRHD], respectively), and male and female rats for
227 104 weeks at doses up to 20 and 15 mg/kg/day, respectively (<1 times exposure at the MRHD).

228

229 Solifenacin succinate had no effect on reproductive function, fertility or early embryonic
230 development of the fetus in male and female mice treated with 250 mg/kg/day (13 times exposure
231 at the MRHD) of solifenacin succinate, and in male rats treated with 50 mg/kg/day (<1 times
232 exposure at the MRHD) and female rats treated with 100mg/kg/day (1.7 times exposure at the
233 MRHD) of solifenacin succinate.

234

235 **Pregnancy, Teratogenic Effects, Pregnancy Category**

236 Pregnancy Category C

237 Reproduction studies have been performed in mice, rats and rabbits. After oral administration of
238 ¹⁴C- solifenacin succinate to pregnant mice, drug-related material has shown to cross the placental
239 barrier. No embryotoxicity or teratogenicity was observed in mice treated with 30 mg/kg/day
240 (1.2 times exposure at the maximum recommended human dose [MRHD]). Administration of
241 solifenacin succinate to pregnant mice, at doses of 100 mg/kg and greater (3.6 times exposure at
242 the MRHD), during the major period of organ development resulted in reduced fetal body
243 weights. Administration of 250 mg/kg (7.9 times exposure at the MRHD) to pregnant mice
244 resulted in an increased incidence of cleft palate. In utero and lactational exposures to maternal
245 doses of solifenacin succinate of 100 mg/kg/day and greater (3.6 times exposure at the MRHD)
246 resulted in reduced peripartum and postnatal survival, reductions in body weight gain, and
247 delayed physical development (eye opening and vaginal patency). An increase in the percentage
248 of male offspring was also observed in litters from offspring exposed to maternal doses of 250
249 mg/kg/day. No embryotoxic effects were observed in rats at up to 50 mg/kg/day (<1 times
250 exposure at the MRHD) or in rabbits at up to 50 mg/kg/day (1.8 times exposure at the MRHD).
251 There are no adequate and well-controlled studies in pregnant women. Because animal
252 reproduction studies are not always predictive of human response, VESicare should be used
253 during pregnancy only if the potential benefit justifies the potential risk to the fetus.

254 **Labor and Delivery**

255 The effect of VESicare on labor and delivery in humans has not been studied.
256 There were no effects on natural delivery in mice treated with 30 mg/kg/day (1.2 times exposure
257 at the maximum recommended human dose [MRHD]). Administration of solifenacin succinate at
258 100 mg/kg/day (3.6 times exposure at the MRHD) or greater increased in peripartum pup
259 mortality.

260 **Nursing Mothers**

261 After oral administration of ¹⁴C-solifenacin succinate to lactating mice, radioactivity was detected
262 in maternal milk. There were no adverse observations in mice treated with 30 mg/kg/day (1.2
263 times exposure at the maximum recommended human dose [MRHD]). Pups of female mice
264 treated with 100 mg/kg/day (3.6 times exposure at the MRHD) or greater revealed reduced body
265 weights, postpartum pup mortality or delays in the onset of reflex and physical development
266 during the lactation period.

267 It is not known whether solifenacin is excreted in human milk. Because many drugs are excreted

268 in human milk, VESicare should not be administered during nursing. A decision should be made
269 whether to discontinue nursing or to discontinue VESicare in nursing mothers.

270

271 **Pediatric Use**

272 The safety and effectiveness of VESicare in pediatric patients have not been established.

273

274 **Geriatric Use**

275 In placebo controlled clinical studies, similar safety and effectiveness were observed between
276 older (623 patients = 65 years and 189 patients = 75 years) and younger patients (1188 patients
277 < 65 years) treated with VESicare. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in
278 special populations)

279

280 **ADVERSE REACTIONS**

281 VESicare has been evaluated for safety in 1811 patients in randomized, placebo-controlled trials.
282 Expected side effects of antimuscarinic agents are dry mouth, constipation, blurred vision
283 (accommodation abnormalities), urinary retention, and dry eyes. The most common adverse
284 events reported in patients treated with VESicare were dry mouth and constipation and the
285 incidence of these side effects was higher in the 10 mg compared to the 5 mg dose group. In the
286 four 12-week double-blind clinical trials, there were three intestinal serious adverse events in
287 patients, all treated with VESicare 10 mg (one fecal impaction, one colonic obstruction, and one
288 intestinal obstruction). The overall rate of serious adverse events in the double-blind trials was
289 2%. Angioneurotic edema has been reported in one patient taking VESicare 5 mg. Compared to
290 twelve weeks of treatment with VESicare, the incidence and severity of adverse events were
291 similar in patients who remained on drug for up to 12 months. The most frequent reason for
292 discontinuation due to an adverse event was dry mouth, 1.5%. Table 6 lists adverse events,
293 regardless of causality, that were reported in randomized, placebo-controlled trials at an incidence
294 greater than placebo and in 1% or more of patients treated with VESicare 5 or 10 mg once daily
295 for up to 12 weeks.

296

297 **Table 6. Percentages of Patients with Treatment-emergent Adverse Events**
 298 **Exceeding Placebo Rate and Reported by 1% or More Patients for Combined**
 299 **Pivotal Studies**
 300

| SYSTEM ORGAN CLASS MedDRA Preferred Term | Placebo | VESicare 5 mg | VESicare 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 |

301

302 **OVERDOSAGE**

303 Acute: Overdosage with VESicare can potentially result in severe anticholinergic effects and
304 should be treated accordingly. The highest VESicare dose given to human volunteers was a
305 single 100 mg dose.

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

310 ***Treatment of Overdosage:*** No cases of acute overdosage have been reported, but in the event of
311 overdose with VESicare treat with gastric lavage and appropriate supportive measures.

312

313 **DOSAGE AND ADMINISTRATION**

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

316 VESicare should be taken with liquids and swallowed whole. VESicare can be administered with
317 or without food.

318

319 ***Dose Adjustment in Renal Impairment***

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

322

323 ***Dose Adjustment in Hepatic Impairment***

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

327

328 ***Dose Adjustment with CYP3A4 Inhibitors***

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

331

331 **HOW SUPPLIED**

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

| | | |
|--------------|--------------|------------|
| 334 strength | 5 mg | 10 mg |
| 335 color | light yellow | light pink |
| 336 debossed | logo, 150 | logo, 151 |

337

| | | |
|------------------|------------------|------------------|
| 338 Bottle of 30 | NDC 51248-150-01 | NDC 51248-151-01 |
|------------------|------------------|------------------|

| | | |
|------------------|------------------|------------------|
| 339 Bottle of 90 | NDC 51248-150-03 | NDC 51248-151-03 |
|------------------|------------------|------------------|

| | | |
|---------------------------|------------------|------------------|
| 340 Unit Dose Pack of 100 | NDC 51248-150-52 | NDC 51248-151-52 |
|---------------------------|------------------|------------------|

341

342 Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59-86°F) [see USP

343 Controlled Room Temperature]

344

345 **Rx only**

346

347 Manufactured by:

348 Yamanouchi Pharma Technologies Inc.

349 Norman, Oklahoma 73072

350

351 Marketed by:

352 Yamanouchi Pharma America, Inc.

353 Paramus, New Jersey 07652

354

355 Marketed and Distributed by:

356 GlaxoSmithKline

357 Research Triangle Park

358 North Carolina 27709

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361 & GlaxoSmithKline

362 [code] November 2004

Patient Information
VESicare[®] - (VES-ih-care)
(solifenacin succinate)

Read the Patient Information that comes with VESicare before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor or other healthcare professional about your condition or treatment. Only your doctor or healthcare professional can determine if treatment with VESicare is right for you.

What is VESicare[®]?

VESicare is a prescription medicine used in adults to treat the following symptoms due to a condition called overactive bladder:

- Having to go to the bathroom too often, also called "urinary frequency",
- Having a strong need to go to the bathroom right away, also called "urgency",
- Leaking or wetting accidents, also called "urinary incontinence."

VESicare has not been studied in children.

What is overactive bladder?

Overactive bladder occurs when you cannot control your bladder contractions. When these muscle contractions happen too often or cannot be controlled, you can get symptoms of overactive bladder, which are urinary frequency, urinary urgency, and urinary incontinence (leakage).

Who should NOT take VESicare[®]?

Do not take VESicare if you:

- are not able to empty your bladder (also called "urinary retention"),
- have delayed or slow emptying of your stomach (also called "gastric retention"),
- have an eye problem called "uncontrolled narrow-angle glaucoma",
- are allergic to VESicare or any of its ingredients. See the end of this leaflet for a complete list of ingredients.

What should I tell my doctor before starting VESicare[®]?

Before starting VESicare tell your doctor or healthcare professional about all of your medical conditions including if you:

- have any stomach or intestinal problems or problems with constipation,
- have trouble emptying your bladder or you have a weak urine stream,
- have an eye problem called narrow angle glaucoma,
- have liver problems,
- have kidney problems,
- are pregnant or trying to become pregnant (It is not known if VESicare can harm your unborn baby.),
- are breastfeeding (It is not known if VESicare passes into breast milk and if it can harm your baby. You should decide whether to breastfeed or take VESicare, but not both.).

Before starting on VESicare, tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. While taking VESicare, tell your doctor or healthcare professional about all changes in the medicines you are taking including prescription and nonprescription medicines, vitamins and herbal supplements. VESicare and other medicines may affect each other.

How should I take VESicare®?

Take VESicare exactly as prescribed. Your doctor will prescribe the dose that is right for you. Your doctor may prescribe the lowest dose if you have certain medical conditions such as liver or kidney problems.

- You should take one VESicare tablet once a day.
- You should take VESicare with liquid and swallow the tablet whole.
- You can take VESicare with or without food.
- If you miss a dose of VESicare, begin taking VESicare again the next day. Do not take 2 doses of VESicare in the same day.
- If you take too much VESicare or overdose, call your local Poison Control Center or emergency room right away.

What are the possible side effects with VESicare®?

The most common side effects with VESicare are:

- blurred vision. Use caution while driving or doing dangerous activities until you know how VESicare affects you.
- dry mouth.
- constipation. Call your doctor if you get severe stomach area (abdominal) pain or become constipated for 3 or more days.
- heat prostration. Heat prostration (due to decreased sweating) can occur when drugs such as VESicare are used in a hot environment.

Tell your doctor if you have any side effects that bother you or that do not go away.

These are not all the side effects with VESicare. For more information, ask your doctor, healthcare professional or pharmacist.

How should I store VESicare®?

- Keep VESicare and all other medications out of the reach of children.
- Store VESicare at room temperature, 50° to 86°F (15° to 30° C). Keep the bottle closed.
- Safely dispose of VESicare that is out of date or that you no longer need.

General information about VESicare

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use VESicare for a condition for which it was not prescribed. Do not give VESicare to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about VESicare. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about VESicare that is written for health professionals. You can also call (866) 972-4636 toll free, or visit www.VESICARE.com.

What are the ingredients in VESicare®?

Active ingredient: solifenacin succinate

Inactive ingredients: lactose monohydrate, corn starch, hypromellose 2910, magnesium stearate, talc, polyethylene glycol 8000 and titanium dioxide with yellow ferric oxide (5 mg VESicare tablet) or red ferric oxide (10 mg VESicare tablet)

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