

3 **Julvelin**

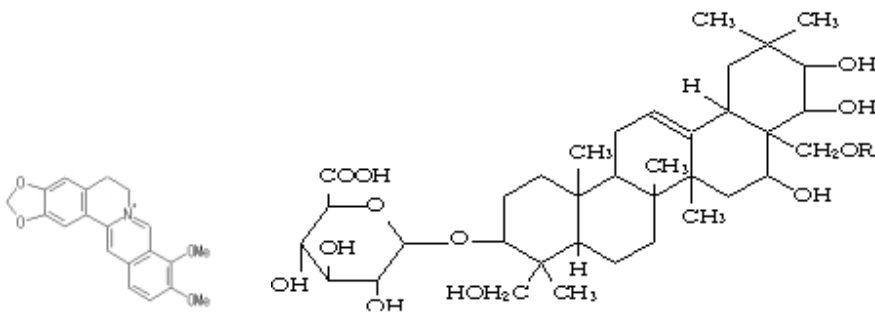
Dietary Supplement  
Diabetes Support Formula

4 **CAPSULES**

5 **OTC**

6 **DESCRIPTION**

7 JULVELIN is a natural antihyperglycemic agent which improves glucose tolerance in patients with  
8 type 2 diabetes, lowering both basal and postprandial plasma glucose. Its composition is  
9 formulated from natural products Berberine and Hcl 220mg, Gymnema sylvestre 220mg,



10  
11 **Berberine HCL**

**Gymnemic Acid**

12 JULVELIN is brownish to white to off-white powder (60 mesh) with a solubility of 2.5mg/ml in pH  
13 5.2 water. Each JULVELIN capsule contains 440mg of the formulated natural components. Each  
14 capsule shell contains gelatin, titanium dioxide and FD&C Blue top white base No. 1.

15 **CLINICAL PHARMACOLOGY**

16 **Mechanism of Action**

17 JULVELIN is a natural antihyperglycemic agent which improves glucose tolerance in patients with  
18 type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic  
19 mechanisms of action are different from other classes of oral antihyperglycemic agents. JULVELIN  
20 decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves  
21 insulin sensitivity by increasing peripheral glucose uptake and utilization. Increased tissue glucose  
22 uptake, liver and muscle glycogen synthesis, inhibition of enzymes involved in glucose production  
23 and enhanced glucose oxidation.

24  
25 JULVELIN with Berberine Acutely Inhibits Insulin Secretion from  $\beta$ -Cells through 3',5'-Cyclic  
26 Adenosine 5'-Monophosphate Signaling Pathway. Berberine, a hypoglycemic agent, has recently

27 been shown to activate AMP-activated protein kinase (AMPK) contributing to its beneficial  
28 metabolic effects in peripheral tissues.

29 However, whether berberine exerts a regulatory effect on  $\beta$ -cells via AMPK or other signaling  
30 pathways and counteracts glucolipotoxicity remains uncertain. In the present study, the impact of  
31 berberine on  $\beta$ -cell function was investigated *in vivo* and *in vitro*. In high-fat-fed rats, berberine  
32 treatment for 6 wk significantly decreased plasma glucose and insulin levels before and after an  
33 oral glucose challenge along with the reduction of body weight and improvement of blood lipid  
34 profile. In accordance with the *in vivo* results, berberine acutely decreased glucose-stimulated  
35 insulin secretion (GSIS) and palmitate-potentiated insulin secretion in MIN6 cells and rat islets.  
36 However, pretreated with berberine for 24 h augmented the response of MIN6 cells and rat islets  
37 to glucose and attenuated the glucolipotoxicity. Berberine acutely increased AMPK activity in  
38 MIN6 cells. However, compound C, an AMPK inhibitor, completely reversed troglitazone-  
39 suppressed GSIS, not berberine-suppressed GSIS. Otherwise, berberine decreased cAMP-raising  
40 agent-potentiated insulin secretion in MIN6 cells and rat islets. These results suggest that the  
41 activation of AMPK is required for troglitazone-suppressed GSIS, whereas cAMP signaling pathway  
42 contributes, at least in part, to the regulatory effect of berberine on insulin secretion.

43

44 The action of berberine was compared with metformin and troglitazone (TZD) with regard to the  
45 glucose-lowering action *in vitro*. HepG2 cell line, phenotypically similar to human hepatocytes, was  
46 used for glucose consumption (GC) studies. Cell proliferation was measured by  
47 methylthiotetrazole (MTT) assay. In moderate high glucose concentration (11.1 mmol/L), GC of  
48 HepG2 cells was increased by 32% to 60% ( $P < .001$  to  $P < .0001$ ) with  $5 \times 10^{-6}$  mol/L to  $1 \times 10^{-4}$   
49 mol/L berberine, which was comparable to that with  $1 \times 10^{-3}$  mol/L metformin. The glucose-  
50 lowering effect of berberine decreased as the glucose concentration increased. The maximal  
51 potency was reached in the presence of 5.5 mmol/L glucose, and it was abolished when the  
52 glucose concentration increased to 22.2 mmol/L. The effect was not dependent on insulin  
53 concentration, which was similar to that of metformin and was different from that of TZD, whose  
54 glucose-lowering effect is insulin dependent. TZD had a better antihyperglycemic potency than  
55 metformin when insulin was added ( $P < .001$ ). In the meantime, a significant toxicity of the drug to  
56 HepG2 cells was also observed. The  $\beta$ TC3 cell line was used for insulin release testing, and no  
57 secretagogue effect of berberine was observed. These observations suggest that berberine is able  
58 to exert a glucose-lowering effect in hepatocytes, which is insulin independent and similar to that  
59 of metformin, but has no effect on insulin secretion.

60 Gymnemic acids from JULVELIN are found to be antidiabetic, and insulinotropic. The active  
61 principles which have been identified as glycosides (several gymnemic acids) suggest that the  
62 topical and selective anaesthetic effect of the acids from plant might result from the reaction of  
63 the receptor sites between glycosides and the sweet substances. Gymnemic acids inhibited glucan  
64 formation by streptococcus mutans *in vivo* and also markedly inhibited the activity of  
65 glucosyltransferase from bacterial coat increasing capillary fragility.

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69 **Pharmacokinetics**

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71 **Absorption**

72 JULVELIN IS well absorbed from an oral dose, with about 70 percent ending up in the  
73 bloodstream. After single oral-dose administration, the maximum observed plasma concentration  
74 (C<sub>max</sub>) of JULVELIN is achieved between 60 minutes and 2 hours (median time of 1 hours).

75 Absolute bioavailability of JULVELIN I following oral dosing has not been determined. The rate and  
76 extent of absorption of JULVELIN are not influenced by food

77

78

79 **Distribution**

80 The mean apparent volume of distribution following oral administration is approximately 52 L,  
81 indicating that JULVELIN is distributed into tissues. At therapeutic concentrations, 94% of JULVELIN  
82 in plasma is bound to proteins. In which radioactivity rapidly appears in liver, kidneys and other  
83 tissues, including the articular cartilage.

84 **Metabolism**

85 JULVELIN metabolism occurs both in nervous tissue and in the liver principally by the cytochrome  
86 P450. JULVELIN by oral administration since the P-gp is expressed in intestinal cells and the  
87 significant first-pass extraction by P450-dependent processes may severely limit its oral  
88 bioavailability.

89

90 **Elimination**

91 Following a single dose of 440mg JULVELIN in normal weight and obese subjects, fecal and urine  
92 excretion of the unabsorbed product was found to be the major route of elimination.  
93 Approximately 86% (range 68% - 95%) of the administered radiolabeled JULVELIN was excreted in  
94 urine and feces over a 7 day collection period with the majority of the dose (72% excreted in the  
95 Urine.

96

97

98 **Special Populations**

99 *Geriatrics:* In studies no difference has been experienced on geriatrics then normal adult  
100 population.

101 *Pediatrics:* After administration of a single oral JULVELIN with food, geometric mean JULVELIN C<sub>max</sub>  
102 and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age)  
103 and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal  
104 function.

105

106

107 Gender: JULVELIN pharmacokinetic parameters did not differ significantly between normal  
 108 subjects and patients with type 2 diabetes when analyzed according to gender (males =  
 109 19, females = 16). Similarly, in controlled clinical studies in patients with type 2 diabetes,  
 110 the antihyperglycemic effect of JULVELIN was comparable in males and females.

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113 **CLINICAL STUDIES**

114 The efficacy and safety of JULVELIN in the treatment of Diabetes Mellitus has been evaluated in 3  
 115 clinical trials (see table 1) of up to 16-week duration, involving over 1260 participants. JULVELIN,  
 116 when taken as needed up to three times per day, was shown to be effective in improving  
 117 sensitivity to insulin and lowering blood sugar levels. Clinical studies also showed significantly  
 118 superior to placebo and similar to metformin.

119

120 In a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese patients with  
 121 type 2 diabetes whose hyperglycemia was not adequately controlled with dietary management  
 122 alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with Julvelin  
 123 (up to 2640 mg/day) for 16 weeks resulted in significant mean net reductions in fasting and  
 124 postprandial plasma glucose (PPG) and hemoglobin A1c (HbA1c) compared to the placebo group  
 125 (see Table 1).

126

127 **Table 1**

	Summary of Mean Changes from Baseline in HbA1c fasting Plasma Glucose (FPG) at Final visit (16 week Study)			
	Placebo	Julvelin 440 mg		
		2 capsules	2 capsules	2 capsules
		One Daily	Twice Daily	3 X Daily
	N=342	N=286	N=362	N=274
<b>Hemoglobin A1c (%)</b>				
Baseline	8.2	8.3	8.4	8.4
Change at mid study point (8wk)	-0.100	-0.700	-0.800	-0.720
Change at Final visit - 16 wk	-0.100	-1.120	-1.300	-1.420
<b>Final A1c</b>	8.10	7.18	7.10	6.98
<b>FPG (mg/dL)</b>				
Baseline	242.0	240.0	241.0	243.0
Change at mid study point (8wk)	-12.0	-47.0	-52.0	-57.6
Change at Final visit - 16 wk	-12.8	-52.0	-68.0	-64.9
	229.20	188.00	173.00	178.10
<b>Mg of Julvelin per day</b>		880	1760	2640

128

129

130 A 40-week, double-blind, placebo-controlled study of JULVELIN and glyburide, alone and in  
 131 combination, was conducted in obese patients with type 2 diabetes who had failed to achieve  
 132 adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately  
 133 240 mg/dL) (see Table 2). Patients randomized to the combination arm started therapy with  
 134 JULVELIN 440 mg and glyburide 20 mg. At the end of each week of the first four weeks of the trial,  
 135 these patients had their dosages of JULVELIN increased by 440 mg if they had failed to reach target

136 fasting plasma glucose. After week four, such dosage adjustments were made monthly, although  
 137 no patient was allowed to exceed JULVELIN 2640 mg. Patients in the JULVELIN only arm (JULVELIN  
 138 plus placebo) followed the same titration schedule. At the end of the trial, approximately 70% of  
 139 the patients in the combination group were taking JULVELIN 2640 mg/glyburide 20 mg or  
 140 JULVELIN 2640 mg/glyburide 20 mg. Patients randomized to continue on glyburide experienced  
 141 worsening of glycemic control, with mean increases in HbA1c and FPG of 0.2% and 13.2 mg/dL,  
 142 respectively. In contrast, those randomized to JULVELIN (up to 2640 mg/day) experienced a slight  
 143 improvement, with mean reductions in HbA1c and FPG of -1.37% and 48.3 mg/dL, respectively.  
 144 The combination of JULVELIN and glyburide was effective in reducing HbA1c and FPG levels of -  
 145 1.42% and 68.4 mg/dL, respectively. Compared to results of glyburide treatment alone, the net  
 146 differences with combination treatment were 1.8% -68 mg/dL, respectively (see Table 2).

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149

150 **Table 2**

	Summary of Study showing Mean Changes from Baseline in FPG, HA1c and Body Weight at final 40 week study with Combined Julvelin/Glyburide vs Glyburide or Julvelin monotherapy		
	Julvelin 440mg	Glyburide 20mg	Julvelin/Glyburide *
Daily Dosage (mg)	2640	20	2640/20
	N=182	N=157	N=217
<b>Hemoglobin A1c (%)</b>			
Baseline	8.3	8.4	8.4
Change at Final visit - 40 wk	-1.370	0.200	-1.420
Final A1c	6.93	8.60	6.98
<b>FPG (mg/dL)</b>			
Baseline	240.0	240.6	239.2
Change at Final visit - 40 wk	-48.3	13.2	-68.4
	191.70	253.80	170.80
<b>Body weight</b>			
Baseline	203.0	205.0	202.0
Change at Final visit - 40 wk	0.4	-0.2	-12

151

\* Combined Julvelin/Glyburide 440mg and 20mg respectively

152 The magnitude of the decline in fasting blood glucose concentration following the institution of  
 153 GLUCOPHAGE (metformin hydrochloride tablets) therapy was proportional to the level of fasting  
 154 hyperglycemia. Patients with type 2 diabetes with higher fasting glucose concentrations  
 155 experienced greater declines in plasma glucose and glycosylated hemoglobin. The mean change in  
 156 Body weight was not significant in any of the three groups.

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160 **Other Clinical Trail evidence**

161 Garvan scientist Dr Jiming Ye says: "Our studies in animal models of diabetes show that berberine  
162 acts in part by activating an enzyme in the muscle and liver that is involved in improving sensitivity  
163 of the tissue to insulin – this in turn helps lower blood sugar levels. In addition it seems berberine  
164 can help reduce body weight". Current medicines for treating type 2 diabetes include metformin  
165 and the TZD group of drugs. However a large number of patients cannot tolerate metformin and  
166 the TZDs can cause undesirable weight gain. Therefore it is critical to develop new therapies to  
167 treat type 2 diabetes which is a growing health problem

168 Research on use of berberine for diabetes began with Ni Yanxi and his colleagues in Changchun (a  
169 large city in Jilin Province) with diabetes treatments. As an introduction to a 1995 English language  
170 publication on this subject (presenting their earlier clinical data from 1983-1987), they wrote (5):  
171 "It was found by accident that berberine had the therapeutic effect on the decrease of blood  
172 glucose when the authors used berberine to treat diarrhea in patients who suffered from  
173 diabetes."

174 Dietary therapy was first introduced to the patients for one month. For those who still had high  
175 fasting blood sugar, berberine was administered orally at a dose of 300, 400, or 500 mg each time,  
176 three times daily, adjusting the dosage according to the blood glucose levels; this treatment was  
177 followed for 1-3 months. A control group without diabetes was similarly treated, with no effect on  
178 blood sugar. For the diabetic patients, it was reported that patients had less thirst, consumed less  
179 water and urinated less, had improved strength, and had lower blood pressure; the symptoms  
180 declined in correspondence with declining blood glucose levels. Laboratory studies suggest that  
181 berberine may have at least two functions in relation to reducing blood sugar: inhibiting  
182 absorption of sugars from the intestine and enhancing production of insulin. As relayed by Ni in his  
183 review of the literature, clinical experience with berberine has shown that doses of 2 grams per  
184 day produced no side effects.

185 Berberine has been shown to regulate glucose and lipid metabolism in vitro and in vivo. This pilot  
186 study was to determine the efficacy and safety of berberine in the treatment of type 2 diabetes  
187 mellitus patients. In study A, 36 adults with newly diagnosed type 2 diabetes mellitus were  
188 randomly assigned to treatment with berberine or metformin (0.5 g 3 times a day) in a 3-month  
189 trial. The hypoglycemic effect of berberine was similar to that of metformin. Significant decreases  
190 in hemoglobin A1c (from 9.5%+/-0.5% to 7.5%+/-0.4%, P<.01), fasting blood glucose (from 10.6+/-  
191 0.9 mmol/L to 6.9+/-0.5 mmol/L, P<.01), postprandial blood glucose (from 19.8+/-1.7 to 11.1+/-0.9  
192 mmol/L, P<.01), and plasma triglycerides (from 1.13+/-0.13 to 0.89+/-0.03 mmol/L, P<.05) were  
193 observed in the berberine group. In study B, 48 adults with poorly controlled type 2 diabetes  
194 mellitus were treated supplemented with berberine in a 3-month trial. Berberine acted by  
195 lowering fasting blood glucose and postprandial blood glucose from 1 week to the end of the trial.  
196 Hemoglobin A1c decreased from 8.1%+/-0.2% to 7.3%+/-0.3% (P<.001). Fasting plasma insulin and  
197 homeostasis model assessment of insulin resistance index were reduced by 28.1% and 44.7%  
198 (P<.001), respectively. Total cholesterol and low-density lipoprotein cholesterol were decreased  
199 significantly as well. During the trial, 20 (34.5%) patients experienced transient gastrointestinal  
200 adverse effects. Functional liver or kidney damages were not observed for all patients. In  
201 conclusion, this pilot study indicates that berberine is a potent oral hypoglycemic agent with  
202 beneficial effects on lipid metabolism.

203

204 **INDICATIONS AND USAGE**

205 JULVELIN is a natural antihyperglycemic agent which improves glucose tolerance in patients with  
206 type 2 diabetes, lowering both basal and postprandial plasma glucose.

207

208

209

210 **CONTRAINDICATIONS**

211 Hypersensitivity to active components.

212

213

214

215 **WARNINGS**

216

217 In most human studies, JULVELIN has been well tolerated for 30 to 160 days.

218 Side effects may include upset stomach, drowsiness, insomnia, headache, skin reactions, sun  
219 sensitivity, and nail toughening. There are rare reports of abdominal pain, loss of appetite,  
220 vomiting, nausea, flatulence (gas), constipation, heartburn, and diarrhea. Based on several human  
221 cases, temporary increases in blood pressure and heart rate, as well as palpitations, may occur  
222 with berberine products. Based on animal research, berberine theoretically may increase the risk  
223 for eye cataract formation.

224

225 **PRECAUTIONS**

226 None Known in pre and post marketing clinical studies.

227 **MISUSE POTENTIAL**

228 No potential for misuse has been experienced in pre marketing clinical studies or during post  
229 marketing events.

230 **USE IN SPECIAL POPULATIONS**

231 **Pregnancy**

232 No adequate and well controlled studies with JULVELIN have been conducted in pregnant women.  
233 Because animal reproductive studies are not always predicative of human response JULVELIN  
234 during pregnancy is not recommended.

235

236 **Nursing Mothers**

237 It is not known if JULVELIN is secreted in human milk. Therefore, JULVELIN should not be taken by  
238 nursing women.

239

240

241 **Pediatric Use**

242 JULVELIN has not been studied in pediatric patients below the age of 12 years. There is not enough  
243 scientific evidence to recommend the use of JULVELIN in children. Avoid in newborns due to  
244 potential for increase in free bilirubin, jaundice, and development of kernicterus (brain damage  
245 caused by severe newborn jaundice).

246

247 **Geriatric Use**

248 Clinical studies of JULVELIN included significant number of patients aged 65 years and older which  
249 determined the resonance was similar to younger patients.

250

251 **ADVERSE REACTIONS**

252 **Clinical Studies Experience**

253 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
254 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of  
255 another drug and may not reflect the rates observed in practice. When taken as recommended in  
256 the placebo-controlled clinical trials, the following adverse events were reported (see Table 3 ) for  
257 JULVELIN:

258

259

260 **Table 3**

Adverse Event	Placebo (N=348)	Summary of Adverse Reactions in case studies over 40 week trial with JULEVIN 440mg		
		2 capsules /day (N=1400)	3 capsules /day (N=853)	4 capsules /day (N=472)
Nausea	3.0%	2.0%	1.0%	3.0%
Vomitting	2.0%	2.0%	2.0%	3.0%
Headache	1.0%	2.0%	2.7%	2.4%
Skin Irritation	1.0%	3.0%	3.2%	2.9%
Facial Flushing	3.0%	3.0%	3.0%	4.0%
Loss os appetite	3.0%	2.0%	5.2%	6.8%
Abdominal tingling effect	2.0%	4.0%	2.0%	3.8%
Hypertension	3.0%	4.6%	2.8%	3.8%

261

262

263 Berberine has been reported to cause nausea, vomiting, hypertension (high blood pressure),  
264 abnormal sensations such as numbness or tingling; however, clinical evidence of such adverse  
265 effects is not prominent in the literature. Rare adverse effects including headache, skin irritation,  
266 facial flushing, headache, bradycardia (slowed heart rate) have also been reported with the use of  
267 berberine. Use cautiously in individuals with hypotension (low blood pressure), as berberine may  
268 have antihypertensive effects.

269 Patients with cardiovascular disease should also use caution as berberine has been associated with  
270 the development of ventricular arrhythmias in subjects with congestive heart failure. Although not  
271 well studied in humans, berberine may also theoretically cause delays in small intestinal transit  
272 time or increase the risk of bleeding.

273 Patients with leukopenia (abnormally low white blood cell count) should use cautiously due to the  
274 potential for development of leukopenia symptoms.

275

## 276 **DRUG-DRUG INTERACTIONS**

277 JULVELIN may counter or prevent irregular heartbeat. Caution is advised when taking JULVELIN  
278 with other agents that alter heart rate.

279 JULVELIN may decrease the efficacy of tetracycline; in theory, JULVELIN may decrease the efficacy  
280 of other agents with antibacterial activity.

281 Berberine bisulfate may stimulate platelet formation, and berberine may have an antiheparin  
282 action. Thus, berberine may interact with certain drugs that increase the risk of bleeding, and  
283 reduce their effectiveness. Some examples include aspirin, anticoagulants ("blood thinners") such  
284 as warfarin (Coumadin<sup>®</sup>) or heparin, anti-platelet drugs such as clopidogrel (Plavix<sup>®</sup>), and non-  
285 steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin<sup>®</sup>, Advil<sup>®</sup>) or naproxen  
286 (Naprosyn<sup>®</sup>, Aleve<sup>®</sup>). However, berberine may be hepatoprotective (liver protective) when  
287 administered before toxic doses of acetaminophen.

288 JULVELIN may lower blood sugar levels. Caution is advised when using medications that may also  
289 lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored  
290 closely by a qualified healthcare professional, including a pharmacist. Medication adjustments may  
291 be necessary.

292 JULVELIN may decrease total and LDL cholesterol, as well as triglycerides. Caution is advised in  
293 patients taking any cholesterol-lowering agents.

294 There may be additive hypotensive (blood pressure lowering) effects and bradycardia (slowed  
295 heart rate) when combining JULVELIN with agents that lower blood pressure. Caution is advised.

296 JULVELIN may modulate the expression and function of PGP-170 in hepatoma cells. In theory,  
297 JULVELIN may interact with antineoplastic agents.

298 Berberine and berberine sulfate have anti-inflammatory effects and may interact with COX-2  
299 inhibitors. COX-2 inhibitor drugs include celecoxib (Celebrex<sup>®</sup>) and rofecoxib (Vioxx<sup>®</sup>).

300

301

## 302 **OVERDOSAGE**

303 Single doses up to 7 grams have not presented any more adverse events than normal dosages.  
304 From clinical studies the likelihood of overdosing is unknown and unlikely.

305

306 **DOSAGE AND ADMINISTRATION**

307 JULVELIN recommended starting dose of 2 capsules per day and may be increased up to 4 capsules  
308 depending on the level of Sugar Levels.

309

310 **Use with Food**

311 JULVELIN may be taken without regard to food. The safety and effectiveness of JULVELIN beyond 3  
312 years have not been determined at this time.

313

314 **USE IN SPECIAL POPULATIONS**

315 **Geriatrics**

316 No dose adjustment is required in patients >65 years of age.

317

318

319 **HOW SUPPLIED**

320 JULVELIN is a dark –blue hard-gelatin capsule containing powder.

321 JULVELIN 440 mg capsules: Dark –blue two piece No. 0 opaque hard –gelatin capsule. – Bottle  
322 containing 120 capsules.

323

324 **Storage Conditions**

325 Store at 25°C (77°F) excursions permitted to 15° to 30°C (59° to 86°F) Keep bottle tightly closed.

326 JULVELIN should not be used after the given expiration date stamped on the top of the lid of each  
327 bottle.

328 Distributed by:



330 Firstmed Pharma, Inc

331 Division of Firstmed Holding Corporation

332 Dothan, AL 33601

333

334 325278

335 Revised May 2007

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