FirstmedPharma

Julvelin

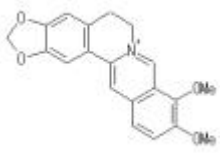
Dietary Supplement
Diabetes Support Formula

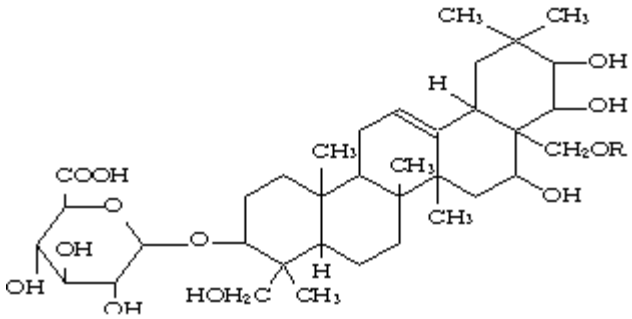
CAPSULES

OTC – Natural Supplement Diabetes Support

DESCRIPTION

JULVELIN is a natural antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its composition is formulated from natural products Berberine and Hcl 200mg, Gymnema sylvestre 100mg, Pyconogenol 100mg, Alpha Lopoic Acid 100mg.





Berberine HCL **Gymnemic Acid**

JULVELIN is brownish to white to off-white powder (60 mesh) with a solubility of 2.5mg/ml in pH 5.2 water. Each JULVELIN capsule contains 500mg of the formulated natural components. Each capsule shell contains gelatin, titanium dioxide and FD&C Blue top white base No. 1.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

JULVELIN with Berberine Acutely Inhibits Insulin Secretion from β-Cells through 3',5'-Cyclic Adenosine 5'-Monophosphate Signaling Pathway. Berberine, a hypoglycemic agent, has recently been shown to activate AMP-activated protein kinase (AMPK) contributing to its beneficial metabolic effects in peripheral tissues.

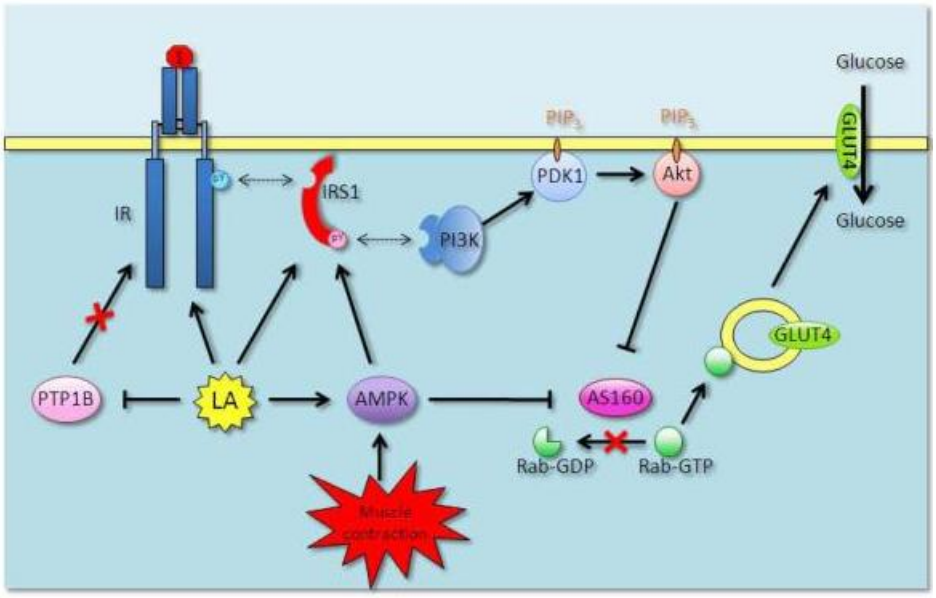
However, whether berberine exerts a regulatory effect on β-cells via AMPK or other signaling pathways and counteracts glucolipotoxicity remains uncertain. In the present study, the impact of berberine on β-cell function was investigated *in vivo* and *in vitro*. In high-fat-fed rats, berberine treatment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

The action of berberine was compared with metformin and troglitazone (TZD) with regard to the glucose-lowering action in vitro. HepG2 cell line, phenotypically similar to human hepatocytes, was used for glucose consumption (GC) studies. Cell proliferation was measured by methylthiotetrazole (MTT) assay. In moderate high glucose concentration (11.1 mmol/L), GC of HepG2 cells was increased by 32% to 60% ($P < .001$ to $P < .0001$) with 5×10^{-6} mol/L to 1×10^{-4} mol/L berberine, which was comparable to that with 1×10^{-3} mol/L metformin. The glucose-lowering effect of berberine decreased as the glucose concentration increased. The maximal potency was reached in the presence of 5.5 mmol/L glucose, and it was abolished when the glucose concentration increased to 22.2 mmol/L. The effect was not dependent on insulin concentration, which was similar to that of metformin and was different from that of TZD, whose glucose-lowering effect is insulin dependent. TZD had a better antihyperglycemic potency than metformin when insulin was added ($P < .001$). In the meantime, a significant toxicity of the drug to HepG2 cells was also observed. The βTC3 cell line was used for insulin release testing, and no secretogogue effect of berberine was observed. These observations suggest that berberine is able to exert a glucose-lowering effect in hepatocytes, which is insulin independent and similar to that of metformin, but has no effect on insulin secretion.

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

Insulin pathway and glucose handling

The interaction of Alpha Lopoic Acid (LA) and intracellular signaling is perceived to account for LA's beneficial effects observed at 24 hours post-administration, a time point that is much delayed from the plasma LA Tmax of ~1 hour. This temporal difference is interesting in light of the rapid metabolism of LA and suggests a different mode of action versus other stimuli that LA mimics. For example, in cultured cells, insulin induced glucose uptake after 10 min. and a maximal effect after 30 min. while LA required 1 hour to induce its maximal effect on glucose uptake, which could be achieved by insulin in half the time. This delay is even evident when comparing the phosphorylation of Akt on Ser473 as induced by insulin versus LA. Such a delay suggests that the effect of LA on glucose handling is not direct but necessitates the activation of additional mediator(s), and also supports the notion that LA or DHLA modulates the IR/PI3K/Akt pathway at different levels.



In skeletal muscle, LA is proposed to recruit GLUT4 from its storage site in the Golgi to the sarcolemma, so that glucose uptake is stimulated by the local increase in transporter abundance. Evidence from cell culture experiments supports the involvement of the insulin-signaling cascade in LA-stimulated translocation of GLUT1 and GLUT4. Klip's group investigated the effects of R- and S-LA on glucose uptake in L6 myotubes and 3T3-L1 adipocytes. R-LA stimulated larger and more rapid glucose uptake than did S-LA or the racemic mixture, and when used in conjunction with insulin, enhanced its glucose uptake action. The cellular distribution of GLUT1 and GLUT4 glucose transporters responded to R-LA in a similar fashion as seen with insulin, and glucose uptake in response to all forms of LA was PI3K-dependent, as determined by use of the inhibitory compound, LY294002. Using the same cell culture models, Moini et al. showed that R-LA stimulated glucose transport for up to 6 hours. While S-LA and the racemic mixture produced the same effect, DHLA did not. R-LA also resulted in tyrosine phosphorylation of the insulin receptor, and glucose uptake was PI3K dependent, as shown by using wortmannin.

Pharmacokinetics

Absorption

JULVELIN IS well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. After single oral-dose administration, the maximum observed plasma concentration (Cmax) of JULVELIN is achieved between 60 minutes and2 hours (median time of 1 hours). Absolute bioavailability of JULVELIN l following oral dosing has not been determined. The rate and extent of absorption of JULVELIN are not influenced by food

Distribution

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

Metabolism

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

Elimination

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

Special Populations

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

Pediatrics: After administration of a single oral JULVELIN with food, geometric mean JUVELIN Cmax and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

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

CLINICAL STUDIES

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

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

Table 1

	Summary of Mean Changes from Baseline in HbA1c fasting Plasma Glocose (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
Hemoglobin A1c (%)				
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
Final A1c	8.10	7.18	7.10	6.98
FPG (mg/dL)				
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
Mg of Julvelin per day		880	1760	2640

A 40-week, double-blind, placebo-controlled study of JULVELIN and glyburide, alone and in combination, was conducted in obese patients with type 2 diabetes who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 240 mg/dL) (see Table 2). Patients randomized to the combination arm started therapy with JULVELIN 440 mg and glyburide 20 mg. At the end of each week of the first four weeks of the trial, these patients had their dosages of JULVELIN increased by 440 mg if they had failed to reach target fasting plasma glucose. After week four, such dosage adjustments were made monthly, although no patient was allowed to exceed JULVELIN 2640 mg. Patients in the JULVELIN only arm (JULVELIN plus placebo) followed the same titration schedule. At the end of the trial, approximately 70% of the patients in the combination group were taking JULVELIN 2640 mg/glyburide 20 mg or

JULVELIN 2640 mg/glyburide 20 mg. Patients randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in HbA1c and FPG of 0.2% and 13.2 mg/dL, respectively. In contrast, those randomized to JULVELIN (up to 2640 mg/day) experienced a slight improvement, with mean reductions in HbA1c and FPG of -1.37% and 48.3 mg/dL, respectively. The combination of JULVELIN and glyburide was effective in reducing HbA1c and FPG levels of -1.42% and 68.4 mg/dL,, respectively. Compared to results of glyburide treatment alone, the net differences with combination treatment were 1.8% -68 mg/dL, respectively (**see Table 2**).

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 monotheraphy		
	Julvelin 440mg	Glyburide 20mg	Julvelin/Glyburide *
Daily Dosage (mg)	2640	20	2640/20
	N=182	N=157	N=217
Hemoglobin A1c (%)			
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
FPG (mg/dL)			
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
Body weight			
Baseline	203.0	205.0	202.0
Change at Final visit - 40 wk	0.4	-0.2	-12

** Combined Julvelin/Glyburide 440mg and 20mg respecfully*

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

Other Clinical Trail evidence

Garvan scientist Dr Jiming Ye says: “Our studies in animal models of diabetes show that berberine acts in part by activating an enzyme in the muscle and liver that is involved in improving sensitivity

of the tissue to insulin – this in turn helps lower blood sugar levels. In addition it seems berberine can help reduce body weight". Current medicines for treating type 2 diabetes include metformin and the TZD group of drugs. However a large number of patients cannot tolerate metformin and the TZDs can cause undesirable weight gain. Therefore it is critical to develop new therapies to treat type 2 diabetes which is a growing health problem

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Hypersensitivity to active components.

WARNINGS

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

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

PRECAUTIONS

None Known in pre and post marketing clinical studies.

MISUSE POTENTIAL

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

USE IN SPECIAL POPULATIONS

Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

Clinical Studies Experience

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

Table 3

		Summary of Adverse Reactions in case studies over 40 week trial with JULEVIN 440mg		
Adverse Event	**Placebo (N=348)**	**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%

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

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

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

DRUG-DRUG INTERACTIONS

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

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

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

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

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

JULVELIN recommended starting dose of 3 capsules per day and may be increased up to 4 capsules depending on the level of Sugar Levels.

Use with Food

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

USE IN SPECIAL POPULATIONS

Geriatrics

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

HOW SUPPLIED

JULVELIN is a dark –blue hard-gelatin capsule containing powder.
JULVELIN 500 mg capsules: Dark –blue two piece No. 0 opaque hard –gelatin capsule. – Bottle containing 90 capsules.

Storage Conditions

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

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

Distributed by:

Firstmed Pharma, Inc
Division of Firstmed Holding Corporation
Dothan, AL 33601

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