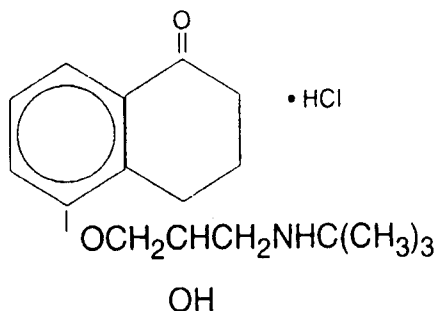


CURRENT LABELING	PROPOSED CHANGES
<p><b>BETAGAN®</b> (levobunolol HCl) Liquifilm® sterile ophthalmic solution with C Cap® Compliance Cap</p>	<p><b>BETAGAN®</b> (levobunolol hydrochloride ophthalmic solution, USP) sterile</p>

### DESCRIPTION

<p><b>DESCRIPTION:</b> BETAGAN® (levobunolol HCl) Liquifilm® sterile ophthalmic solution is a noncardioselective beta-adrenoceptor blocking agent for ophthalmic use.</p>	<p><b>DESCRIPTION: BETAGAN®</b> (levobunolol hydrochloride ophthalmic solution, USP) sterile is a noncardioselective beta-adrenoceptor blocking agent for ophthalmic use. The solution is colorless to slightly light yellow in appearance with an osmolality range of of 250-360 mOsm/kg. The shelf life pH range is 5.5 to 7.5</p>
<p><b>CHEMICAL NAME: Levobunolol HCl:</b> (-)-5-[3-(tert-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2H)-naphthalenone hydrochloride.</p>	<p>NONE</p>

**STRUCTURAL FORMULA:** Levobunolol HCl



<p><b>CONTAINS:</b> BETAGAN® 0.25% and 0.5% contains – Active: levobunolol HCl 0.25% or 0.5%. Preservative: benzalkonium chloride 0.004%. Inactives: Liquifilm® (polyvinyl alcohol) 1.4%; edetate disodium; sodium metabisulfite; sodium phosphate, dibasic; potassium phosphate, monobasic; sodium chloride; hydrochloric acid or sodium hydroxide to adjust pH; and purified water.</p>	<p><b>Contains:</b> <b>Active:</b> levobunolol HCl 0.25% or 0.5%. <b>Preservative:</b> benzalkonium chloride 0.004%. <b>Inactives:</b> polyvinyl alcohol 1.4%; edetate disodium; sodium metabisulfite; sodium phosphate, dibasic; potassium phosphate, monobasic; sodium chloride; hydrochloric acid or sodium hydroxide to adjust pH; and purified water.</p>
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### CLINICAL PHARMACOLOGY

<p><b>CLINICAL PHARMACOLOGY:</b> Levobunolol HCl is a noncardioselective beta-adrenoceptor blocking agent, equipotent at both beta<sub>1</sub> and beta<sub>2</sub> receptors. Levobunolol HCl is greater than 60 times more potent than its dextro isomer in its beta- blocking activity, yet equipotent in its potential for direct myocardial depression. Accordingly, the levo isomer, levobunolol HCl, is used. Levobunolol HCl does not have significant local anesthetic (membrane-stabilizing) or intrinsic sympathomimetic activity.</p>	<p>NONE</p>
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Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.	NONE
Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed para-sympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.	NONE
BETAGAN® (levobunolol HCl) has been shown to be an active agent in lowering elevated as well as normal intraocular pressure (IOP) whether or not accompanied by glaucoma. Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.	BETAGAN® (levobunolol hydrochloride ophthalmic solution USP) has been shown to be an active agent in lowering elevated as well as normal intraocular pressure (IOP) whether or not accompanied by glaucoma. Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.
The onset of action with one drop of BETAGAN® can be detected within one hour after treatment, with maximum effect seen between 2 and 6 hours.	NONE
A significant decrease of IOP can be maintained for up to 24 hours following a single dose.	NONE
In two, separate, controlled studies (one three month and one up to 12 months duration) BETAGAN® 0.25% b.i.d. controlled the IOP of approximately 64% and 70% of the subjects. The overall mean decrease from baseline was 5.4 mm Hg and 5.1 mm Hg respectively. In an open-label study, BETAGAN® 0.25% q.d. controlled the IOP of 72% of the subjects while achieving an overall mean decrease of 5.9 mm Hg.	Add the words "ophthalmic solution" after the trade name of BETAGAN®
In controlled clinical studies of approximately two years duration, intraocular pressure was well-controlled in approximately 80% of subjects treated with BETAGAN® 0.5% b.i.d. The mean IOP decrease from baseline was between 6.87 mm Hg and 7.81 mm Hg. No significant effects on pupil size, tear production or corneal sensitivity were observed. BETAGAN® at the concentrations tested, when applied topically, decreased heart rate and blood pressure in some patients. The IOP-lowering effect of BETAGAN® was well maintained over the course of these studies	Add the words "ophthalmic solution" after first use of the trade name BETAGAN® in paragraph
In a three month clinical study, a single daily application of 0.5% BETAGAN® controlled the IOP of 72% of subjects achieving an overall mean decrease in IOP of 7.0 mm Hg.	Add the words "ophthalmic solution" after the trade name BETAGAN®
The primary mechanism of the ocular hypotensive action of levobunolol HCl in reducing IOP is most likely a decrease in aqueous humor production. BETAGAN® reduces IOP with little or no effect on pupil size or accommodation in contrast to the miosis which cholinergic agents are known to produce. The blurred vision and night blindness often associated with miotics would not be expected and have not been reported with the use of BETAGAN®. This is particularly important in cataract patients with central lens opacities who would experience decreased visual acuity with pupillary constriction.	NONE

### INDICATIONS AND USAGE

<b>INDICATIONS AND USAGE:</b> BETAGAN® has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma or ocular hypertension.	Add the words "ophthalmic solution" after the trade name BETAGAN®
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### CONTRAINDICATIONS

<b>CONTRAINDICATIONS:</b> BETAGAN® is contraindicated in those individuals with bronchial asthma, or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second and third degree atrioventricular block; overt	Add the words "ophthalmic solution" after the trade name BETAGAN®
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cardiac failure (see WARNINGS); cardiogenic shock; or hypersensitivity to any component of these products.

### WARNINGS

<p><b>WARNINGS:</b> As with other topically applied ophthalmic drugs, BETAGAN® may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents [See CONTRAINDICATIONS].</p>	<p>NONE</p>
<p><b>Cardiac Failure:</b> Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.</p>	<p>NONE</p>
<p><b>In Patients without a History of Cardiac Failure:</b> Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, BETAGAN® should be discontinued.</p>	<p>Add the words "ophthalmic solution" after the trade name BETAGAN®</p>
<p><b>Obstructive Pulmonary Disease:</b> PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR A HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR A HISTORY OF BRONCHIAL ASTHMA, IN WHICH BETAGAN® IS CONTRAINDICATED, See CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING BETAGAN. However, if BETAGAN® is deemed necessary in such patients, then it should be administered cautiously since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta<sub>2</sub> receptors.</p>	<p>NONE</p>
<p><b>Major Surgery:</b> The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic blocking agents may be appropriate.</p> <p>If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE).</p>	<p>NONE</p>
<p><b>Diabetes Mellitus:</b> Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.</p>	<p>NONE</p>
<p><b>Thyrotoxicosis:</b> Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.</p>	<p>NONE</p>
<p>These products contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.</p>	<p>NONE</p>

### PRECAUTIONS

<p><b>PRECAUTIONS: General:</b> BETAGAN® should be used with caution in patients with known hypersensitivity to other beta-adrenoceptor blocking agents.</p>	<p>Add the words "ophthalmic solution" after the trade name BETAGAN®</p>
<p>Use with caution in patients with known diminished pulmonary function.</p>	<p>NONE</p>

BETAGAN® should be used with caution in patients who are receiving a beta-adrenergic blocking agent orally, because of the potential for additive effects on systemic beta-blockade or on intraocular pressure. Patients should not typically use two or more topical ophthalmic beta-adrenergic blocking agents simultaneously.	NONE
Because of the potential effects of beta-adrenergic blocking agents on blood pressure and pulse rates, these medications must be used cautiously in patients with cerebrovascular insufficiency. Should signs or symptoms develop that suggest reduced cerebral blood flow while using BETAGAN®, alternative therapy should be considered.	Add the words "ophthalmic solution" after the trade name BETAGAN®
In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires, in most cases, constricting the pupil with a miotic. BETAGAN® has little or no effect on the pupil. When BETAGAN® is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be followed with a miotic and not alone.	Add the words "ophthalmic solution" after the first use of trade name BETAGAN® in paragraph
<b>Muscle Weakness:</b> Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).	NONE
<b>Drug Interactions:</b> Although BETAGAN® used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETAGAN® and epinephrine may occur.	Add the words "ophthalmic solution" after the first use of trade name BETAGAN® in paragraph
Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.	NONE
Patients receiving beta-adrenergic blocking agents along with either oral or intravenous calcium antagonists should be monitored for possible atrioventricular conduction disturbances, left ventricular failure and hypotension. In patients with impaired cardiac function, simultaneous use should be avoided altogether.	NONE
The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects on prolonging atrioventricular conduction time.	NONE
Phenothiazine-related compounds and beta-adrenergic blocking agents may have additive hypotensive effects due to the inhibition of each other's metabolism.	NONE
<b>Risk of anaphylactic reaction:</b> While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.	Change "reaction" to "reactions" in paragraph per FDA request.
<b>Animal Studies:</b> No adverse ocular effects were observed in rabbits administered BETAGAN® topically in studies lasting one year in concentrations up to 10 times the human dose concentration.	Add the words "ophthalmic solution" after the trade name BETAGAN®
<b>Carcinogenesis, mutagenesis, impairment of fertility:</b> In a lifetime oral study in mice, there were statistically significant ( $p \leq 0.05$ ) increases in the incidence of benign leiomyomas in female mice at 200 mg/kg/day (14,000 times the recommended human dose for glaucoma), but not at 12 or 50 mg/kg/day (850 and 3,500 times the human dose). In a two year oral study of levobunolol HCl in rats, there was a statistically significant ( $p \leq 0.05$ ) increase in the incidence of benign hepatomas in male rats administered 12,800 times the recommended human dose for glaucoma. Similar differences were not observed in rats administered oral doses equivalent to 350 times to 2,000 times the recommended human dose for glaucoma.	NONE
Levobunolol did not show evidence of mutagenic activity in a battery of microbiological and mammalian <i>in vitro</i> and <i>in vivo</i> assays.	NONE
Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 1,800 times the recommended human dose for glaucoma.	NONE

<b>Pregnancy category C:</b> Fetotoxicity (as evidenced by a greater number of resorption sites)	<b>Pregnancy: Pregnancy category C.</b>
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has been observed in rabbits when doses of levobunolol HCl equivalent to 200 and 700 times the recommended dose for the treatment of glaucoma were given. No fetotoxic effects have been observed in similar studies with rats at up to 1,800 times the human dose for glaucoma. Teratogenic studies with levobunolol in rats at doses up to 25 mg/kg/day (1,800 times the recommended human dose for glaucoma) showed no evidence of fetal malformations. There were no adverse effects on postnatal development of offspring. It appears when results from studies using rats and studies with other beta-adrenergic blockers are examined, that the rabbit may be a particularly sensitive species. There are no adequate and well-controlled studies in pregnant women. BETAGAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	revised per FDA request Add the words "ophthalmic solution" after the trade name BETAGAN®
<b>Nursing mothers:</b> It is not known whether this drug is excreted in human milk. Systemic beta-blockers and topical timolol maleate are known to be excreted in human milk. Caution should be exercised when BETAGAN® is administered to a nursing woman.	NONE
<b>Pediatric use:</b> Safety and effectiveness in pediatric patients have not been established.	NONE
	<b>Geriatric use:</b> No overall differences in safety or effectiveness have been observed between elderly and younger patients.

### ADVERSE REACTIONS

<b>ADVERSE REACTIONS:</b> In clinical trials the use of BETAGAN® has been associated with transient ocular burning and stinging in up to 1 in 3 patients, and with blepharoconjunctivitis in up to 1 in 20 patients. Decreases in heart rate and blood pressure have been reported (see CONTRAINDICATIONS and WARNINGS).	Add the words "ophthalmic solution" after the trade name BETAGAN®
The following adverse reactions have been reported rarely with the use of BETAGAN®: iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus.	NONE
Increased corneal sensitivity has been noted in a small number of patients. Although levobunolol has minimal membrane-stabilizing activity, there remains a possibility of decreased corneal sensitivity after prolonged use.	NONE
The following additional adverse reactions have been reported either with BETAGAN® or ophthalmic use of other beta-adrenergic receptor blocking agents:	Add the words "ophthalmic solution" after the trade name BETAGAN®
<b>BODY AS A WHOLE:</b> Headache, asthenia, chest pain. <b>CARDIOVASCULAR:</b> Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, congestive heart failure, palpitation, cardiac arrest. <b>DIGESTIVE:</b> Nausea, diarrhea. <b>PSYCHIATRIC:</b> Depression, confusion, increase in signs and symptoms of myasthenia gravis, paresthesia. <b>SKIN:</b> Hypersensitivity, including localized and generalized rash, alopecia, Stevens-Johnson syndrome. <b>RESPIRATORY:</b> Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion. <b>UROGENITAL:</b> Impotence. <b>ENDOCRINE:</b> Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). <b>SPECIAL SENSES:</b> Signs and symptoms of keratitis, blepharoptosis, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.	NONE
Other reactions associated with the oral use of non-selective adrenergic receptor blocking agents should be considered potential effects with ophthalmic use of these agents.	NONE

### OVERDOSAGE

<b>OVERDOSAGE:</b> No data are available regarding overdosage in humans. Should accidental ocular overdosage occur, flush eye(s) with water or normal saline. If accidentally ingested, efforts to decrease further absorption may be appropriate (gastric lavage). The most common signs and symptoms to be expected with overdosage with administration of a systemic beta-adrenergic blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac	NONE
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failure. Should these symptoms occur, discontinue BETAGAN® therapy and initiate appropriate supportive therapy. The following supportive measures should be considered:	
1. Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 mg to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker should be considered.	NONE
2. Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride may be useful.	NONE
3. Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.	NONE
4. Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon hydrochloride which may be useful.	NONE
5. Heart block (second or third degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.	NONE

### DOSAGE AND ADMINISTRATION

<p><b>DOSAGE AND ADMINISTRATION:</b> The recommended starting dose is one to two drops of BETAGAN® 0.5% in the affected eye(s) once a day. Typical dosing with levobunolol HCl 0.25% is one to two drops twice daily. In patients with more severe or uncontrolled glaucoma, BETAGAN® 0.5% can be administered b.i.d. As with any new medication, careful monitoring of patients is advised. Dosages above one drop of BETAGAN® 0.5% b.i.d. are not generally more effective. If the patient's IOP is not at a satisfactory level on this regimen, concomitant therapy with dipivefrin and/or epinephrine, and/or pilocarpine and other miotics, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted. Patients should not typically use two or more topical ophthalmic beta-adrenergic blocking agents simultaneously.</p>	Add the words "ophthalmic solution" after first use of the trade name BETAGAN®
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### HOW SUPPLIED

<p>BETAGAN® (levobunolol HCl) Liquifilm® sterile ophthalmic solution is supplied sterile in white opaque plastic dropper bottles as follows:</p>			<p><b>BETAGAN® (levobunolol hydrochloride ophthalmic solution, USP)</b> is supplied sterile in white low density polyethylene ophthalmic dispenser bottles and tips.</p> <p><b>BETAGAN® 0.25%</b> strength units include a light blue high intensity polystyrene cap.</p> <p><b>BETAGAN® 0.5%</b> strength units include a yellow high intensity polystyrene cap.</p>
<p><b>BETAGAN® 0.25%</b></p>	<p>C Cap® Compliance Cap BID (twice daily)</p> <p>5 mL-NDC 11980-469-25      10 mL- NDC 11980-469-20</p>	<p><b>BETAGAN® 0.25%</b></p> <p>5 mL fill in 10mL bottle    NDC 0023-4526-05  10 mL fill in 15mL bottle    NDC 0023-4526-10</p>	
<p><b>BETAGAN® 0.5%</b></p> <p>Standard Cap</p> <p>2mL-NDC 11980-252-02</p>	<p>C Cap® Compliance Cap      C Cap® Compliance Cap</p> <p>Q.D. (once daily)                      BID (twice Daily)</p> <p>5mL- NDC 11980-252-65      5mL- NDC 11980-252-25  10mL- NDC 11980-252-60      10mL- NDC 11980-252-20  15mL- NDC 11980-252-61      15mL- NDC 11980-252-21</p>	<p><b>BETAGAN® 0.5%</b></p> <p>2 mL fill in 6mL bottle    NDC 0023-4385-02  5 mL fill in 10mL bottle    NDC 0023-4385-05  10 mL fill in 15mL bottle    NDC 0023-4385-10  15 mL fill in 15mL bottle    NDC 0023-4385-15</p>	
<p><b>OTE:</b> Protect from light. Store at controlled room temperature 15°-30°C (59°-86°F)</p>			<p><b>NOTE:</b> Protect from light. Store at 15°-30°C (59°-86°F)</p>
<p><b>Caution:</b> Federal (U.S.A.) law prohibits dispensing without prescription.</p>			<p><b>Rx only</b></p>

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<b>C CAP® COMPLIANCE CAP Patient instructions</b>	DELETE
<b>INSTRUCTIONS FOR USE:</b>	DELETE
1. On the first usage, make sure the number "1" or the correct day of the week appears in the window. If not, click the cap to the right station.	DELETE
2. Remove the cap and apply the medication.	
3. Replace the cap. Hold the C Cap® between your thumb and forefinger. Now rotate the bottle until the cap clicks to the next station.	DELETE
4. When it's time to take your next dose, repeat steps 2 and 3.	
Don't try to catch up on missed doses by applying more than one dose at a time. Each time you replace the cap, turn it until you hear the click. The number in the window specifies your next dosage.	DELETE

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