Triamcinolone compositions, and methods of using such compositions, useful for injection into the vitreous of human eyes or into a joint are provided. Such compositions can include triamcinolone particles present in a therapeutically effective amount, a viscosity inducing component, and an aqueous carrier component. The compositions have viscosities of at least about 10 cps or about 100 cps at a shear rate of 0.1/second. In a preferred embodiment, the viscosity is in the range of from about 80,000 cps to about 300,000 cps. In a most preferred embodiment, the viscosity is in the range of from about 140,000 cps to about 280,000 cps at a shear rate of 0.1/second at 25°C. The compositions advantageously suspend the triamcinolone particles for prolonged periods of time.
LOW IMMUNOGENICITY CORTICOSTEROID COMPOSITIONS

CROSS REFERENCE

[0001] This application is a continuation in part of application Ser. No. 11/354,415, filed Feb. 14, 2006, which is a continuation in part of application Ser. No. 10/966,764, filed Oct. 14, 2004, which application claims the benefit of provisional patent application Ser. No. 60/519,237, filed Nov. 12, 2003 and provisional is patent application Ser. No. 60/530,062, filed Dec. 16, 2003, all of which applications are hereby incorporated herein by reference in their entireties.

BACKGROUND

[0002] The present invention relates to corticosteroid compositions and methods for treating and/or preventing ocular conditions, such as anterior ocular conditions and posterior ocular conditions, as well as for treating various articular pathologies. In particular, the present invention relates to extended release and sustained release triamcinolone compositions, including injectable implants, for treating posterior ocular conditions, as well as for treating joint inflammation and/or joint pain.

[0003] A pharmaceutical composition (synonymously a composition) is a formulation which contains at least one active ingredient (for example a corticosteroid such as a triamcinolone) as well as, for example, one or more excipients, buffers, carriers, stabilizers, preservatives and/or bulking agents, and is suitable for administration to a patient to achieve a desired effect or result. The pharmaceutical compositions disclosed herein can have diagnostic, therapeutic, cosmetic and/or research utility in various species, such as for example in human patients or subjects.

[0004] An ocular condition can include a disease, ailment or condition which affects or involves the eye or one of the parts or regions of the eye. Broadly speaking the eye includes the eyeball and the tissues and fluids which constitute the eyeball, the periocular muscles (such as the oblique and rectus muscles) and the portion of the optic nerve which is within or adjacent to the eyeball. An anterior ocular condition is a disease, ailment or condition which affects or involves an anterior (i.e. front of the eye) ocular region or site, such as a pericocular muscle, an eye lid or an eye ball tissue or fluid which is located anterior to the posterior wall of the lens capsule or ciliary muscles. Thus, an anterior ocular condition primarily affects or involves, the conjunctiva, the cornea, the conjunctiva, the anterior chamber, the iris, the posterior chamber (behind the retina but in front of the posterior wall of the lens capsule), the lens or the lens capsule and blood vessels and nerve which vascularize or innervate an anterior ocular region or site. A posterior ocular (also referred to herein synonymously as a "posterior segment") condition is a disease, ailment or condition which primarily affects or involves a posterior ocular region or site such as choroid or sclera (in a position posterior to a plane through the posterior wall of the lens capsule), vitreous, vitreous chamber, retina, optic nerve (i.e. the optic disc), and blood vessels and nerves which vascularize or innervate a posterior ocular (or posterior segment) region or site.

[0005] Thus, a posterior ocular condition can include a disease, ailment or condition, such as for example, macular degeneration (such as non-exudative age related macular degeneration and exudative age related macular degeneration); choroidal neovascularization; acute macular neuroretinopathy; macular edema (such as cystoid macular edema and diabetic macular edema); Behcet’s disease, retinal disorders, diabetic retinopathy (including proliferative diabetic retinopathy); retinal arterial occlusive disease; central retinal vein occlusion; uveitis (including intermediate and anterior uveitis); retinal detachment; ocular trauma which affects a posterior ocular site or location; a posterior ocular condition caused by or influenced by an ocular laser treatment; posterior ocular conditions caused by or influenced by a photodynamic therapy; photoacogulation; radiation retinopathy; epiretinal membrane disorders; branch retinal vein occlusion; posterior ischemic optic neuropathy; non-retinopathy diabetic retinal dysfuction, retinitis pigmentosa and glaucoma. Glaucoma can be considered a posterior ocular condition because a therapeutic goal can be to prevent the loss of or reduce the occurrence of loss of vision due to damage to or loss of retinal cells or optic nerve cells (i.e. neuroprotection).

[0006] An anterior ocular condition can include a disease, ailment or condition, such as for example, aphakia; pseudophakia; astigmatism; blepharospasm; cataract; conjunctival diseases; conjunctivitis; corneal diseases; corneal ulcer; dry eye syndromes; eyelid diseases; lacrimal apparatus diseases; lacrimal duct obstruction; myopia; presbyopia; pupil disorders; refractive disorders and strabismus. Glaucoma can also be considered to be an anterior ocular condition because a clinical goal of glaucoma treatment can be to reduce a hypertension of aqueous fluid in the anterior chamber of the eye (i.e. reduce intraocular pressure).

[0007] Macular edema is a major cause of visual loss in patients with diabetes, central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). Although laser photoacogulation can reduce further vision loss in patients with diabetic macular edema (DME), vision that has already been decreased by macular edema usually does not improve by use of laser photoacogulation. Currently, there is no FDA (U.S. Food and Drug Administration) approved treatment for macular edema associated with CRVO. For macular edema associated with BRVO, grid laser photoacogulation may be an effective treatment for some patients.

[0008] Diabetic macular edema results from abnormal leakage of macromolecules, such as lipoproteins, from retinal capillaries into the extravascular space followed by an oncotic influx of water into the extravascular space. Abnormalities in the retinal pigment epithelium may also cause or contribute to diabetic macular edema. These abnormalities can allow increased fluid from the chorio-capillaries to enter the retina or they may decrease the normal efflux of fluid from the retina to the chorio-capillaries. The mechanism of breakdown of the blood-retina barrier at the level of the retinal capillaries and the retinal pigment epithelium may be due to changes to tight junction proteins such as occludin. Antcliff R., et al Marshall J., The pathogenesis of edema in diabetic maculopathy, Semia Ophthalmol 1999; 14:223-232.

[0009] Macular edema from venous occlusive disease can result from thrombus formation at the lamina cribrosa or at an arteriovenous crossing. These changes can result in an increase in retinal capillary permeability and accompanying retinal edema. The increase in retinal capillary permeability
and subsequent retinal edema can ensue from a breakdown of the blood retinal barrier mediated in part by vascular endothelial growth factor (VEGF), a 45 kD glycoprotein, as it is known that VEGF can increase vascular permeability. VEGF may regulate vessel permeability by increasing phosphorylation of tight junction proteins such as occludin and zonula occludens. Similarly, in human non-ocular disease states such as ascites, VEGF has been characterized as a potent vascular permeability factor (VPF).

[0010] The normal human retina contains little or no VEGF; however, hypoxia causes upregulation of VEGF production. Disease states characterized by hypoxia-induced VEGF upregulation include CRVO and BRVO. This hypoxia induced upregulation of VEGF can be inhibited pharmacologically. Pe'er I. et al., Vascular endothelial growth factor upregulation in human central retinal vein occlusion, Ophthalmology 1998; 105:412-416. It has been demonstrated that anti-VEGF antibodies can inhibit VEGF driven capillary endothelial cell proliferation. Attenuation of the effects of VEGF introduces a rationale for treatment of macular edema from venous occlusive disease.

[0011] Corticosteroids, a class of substances with anti-inflammatory properties, have been demonstrated to inhibit the expression of the VEGF gene. Nauck M. et al., Induction of vascular endothelial growth factor by platelet-activating factor and platelet-derived growth factor is downregulated by corticosteroids, Am J Resp Cell Mol Biol 1997; 16:398-406. Additionally, corticosteroids can downregulate the induction of VEGF by the pro-inflammatory mediators PDGF and platelet-activating factor (PAF) in a time and dose-dependent manner. Nauck M. et al., Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells, Euro J Pharmacol 1998; 341:309-315. Thus, corticosteroids can down-regulate VEGF production and reduce breakdown of the blood-retinal barrier. Certain steroids can also have antiangiogenic properties possibly due to attenuation of the effects of VEGF. It should be noted that although certain corticosteroids can apparently down regulate VEGF production there are a number of other physiological mechanisms by which corticosteroids can effect the pathogenesis of an ocular condition, such as macular edema.

[0012] Triamcinolone

[0013] Triamcinolone is a corticosteroid and it has been reported that a saline suspension is of triamcinolone (1 mg triamcinolone acetonide in 0.1 ml saline) is non-toxic upon intravitreal injection. McCuen B. et al., The lack of toxicity of intravitreally administered triamcinolone acetonide, Am J Ophthalmol 1981; 91:785-788. Intravitreal triamcinolone has been used to treat proliferative vitreoretinopathy (Jonas J. et al., Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy, Br J Ophthalmol 2000; 84:1064-1067), as well as choroidal neovascularization (Chaila J. et al., Exudative macular degeneration and intravitreal triamcinolone: 18 month follow up, Aust N Z J Ophthalmol 1998; 26:277-281; Penfield P. et al., Exudative macular degeneration and intravitreal triamcinolone: A pilot study, Aust N Z J Ophthalmol 1995; 23:293-298, and; Danis R. et al., Intravitreal triamcinolone acetonide in exudative age-related macular degeneration, Retina 2000; 20:244-250).


[0015] Known formulations of triamcinolone clear (diffuses out of and/or is removed by one or more active transport mechanisms) from the vitreous within at most about 90 days, although it has been speculated that with a known formulation (Kenalog) the triamcinolone may be detectable in the vitreous for no more than four months after intravitreal injection. Thus, McCuen B. et al. (1981) supra at page 786 noted that after three months no triamcinolone was visible in any treated eyes. Others have reported that the triamcinolone present in a saline or other aqueous suspension or solution is upon intravitreal administration cleared from the vitreous in about 21-41 days; using ophthalmoscopic and spectrophotometric detection means to determine disappearance of the injected triamcinolone, in non-vitrectomized rabbit eyes the average clearance rate of intravitreally triamcinolone (0.5 mg) was 41 days, while in eyes having undergone vitrectomy or combination vitrectomy and lensectomy the average clearance rate was 17 days and 7 days, respectively. Schindler R. et al., The clearance of intravitreal triamcinolone acetate, Am J Ophthalmol 1982; 93:415-417. Using high-performance liquid chromatography (HPLC) complete clearance of intravitreally injected triamcinolone (0.4 mg) in 24 rabbit eyes was observed by 21 days. Scholes G. et al., Clearance of triamcinolone from vitreous, Arch Ophthalmol 1985; 103:1567-1569.). Such rapid clearance from the vitreous can necessitate frequent re-administration (re-dosing) in order to effectively treat an ocular condition.

[0016] A triamcinolone pharmaceutical composition available under the trade name Kenalog® (Bristol-Myers-Squibb, Princeton N.J.) has been widely used off-label to treat various ocular conditions, including by intravitreal administration. Significantly, Kenalog® is approved by the U.S. Food and Drug Administration only for intramuscular or intrabursal use, but not for the treatment of any ocular conditions. Each milliliter (ml) of Kenalog® 40 composition comprises 40 milligrams (mg) of triamcinolone acetonide, sodium chloride as a tonicity agent, 10 mg (0.99%) benzyl alcohol as a preservative, 7.5 mg (0.75%) of carboxymethylcellulose sodium and 0.4 mg (0.04%) of polysorbate 80 as resuspension aids.

[0017] It has been reported that Kenalog has a 15 day half life in the vitreous with an effect on central macular thickness being observed for up to 140 days after intravitreal injection of the Kenalog. Aubren, F. et al., Pharmacokinetic-Pharmacodynamic modeling of the effect of Triamcinolone...
Noninfectious endophthalmitis have been reported upon intravitreal Kenalog®, injection, possibly related to the preservative excipients and/or resuspension aids present in Kenalog® (Roth D. et al., Noninfectious endophthalmitis associated with intravitreal triamcinolone injection, Arch Ophthalmol 2003; 121: 1279-1282; Sutter F. et al., Pseudo-endophthalmitis after intravitreal injection of triamcinolone, Br J Ophthalmol 2003; 87:972-974).

Additionally, the presence of benzyl alcohol preservative and polysorbate 80 surfactant in Kenalog® can potentially damage or be toxic to sensitive ocular tissues, such as retinal cells, and for this reason clinicians routinely wash the triamcinolone acetonide precipitate (which forms when Kenalog® is left standing) several times with saline to reduce the concentration of these undesirable non-active materials from the formulation. Additionally, methods have been developed to filter out of Kenalog® and from identical formulations such as Kenacort-A the preservative surfactant, and/or resuspension (suspending agents) aids present in these formulations. Nishimura A. et al., Isolating Triamcinolone acetonide particles for intravitreal use with a porous membrane filter, Retina, vol 23(9): 777-779 (2003). Such washing and/or filtering steps are inconvenient, time consuming, and increase the possibility of microbial or endotoxin contamination that could lead to intraocular infection and inflammation.

Significantly, the triamcinolone acetonide in Kenalog® 40 tends to rapidly separate and precipitate from the remainder of the composition. For example, if Kenalog® is left standing for as short a time as about five to ten minutes a substantial separation of a triamcinolone acetonide precipitate from the remainder of the composition occurs. Unfortunately, such rapid settling of the triamcinolone also occurs with other known saline based suspensions of triamcinolone (with or with preservatives and stabilizers). Thus, if the composition is to be injected into the eye it must first be vigorously shaken and used promptly after being so shaken in order to provide a substantially uniform suspension. A substantially uniform suspension (which is not provided by Kenalog or other saline based suspensions of triamcinolone) is required in order to provide a consistent and accurate dose upon administration of the suspension to the eye. In addition, resuspension processing requires the use of the resuspension aids noted above, at least one of which is less than totally desirable for sensitive ocular tissues. At least because of the potential risk of noninfectious endophthalmitis from use of the Kenalog® vehicle, development of a preservative-free triamcinolone formulation for intravitreal use to treat an ocular condition (such as a posterior ocular condition) is desirable.

Elevated intraocular pressure, that is elevated anterior chamber intraocular pressure, depends on the comparative rates of aqueous production and aqueous drainage, primarily through the trabecular meshwork. Increased intraocular pressure occurs from a variety of mechanisms such as primary or secondary angle-closure glaucoma, primary or secondary open-angle glaucoma, or combined-mechanism glaucoma. If inadequately treated, increased intraocular pressure may result in glaucomatous optic nerve changes and loss of visual field.

Known formulations of corticosteroids administered by a topical, systemic or peribulbar route can cause an increase in anterior chamber intraocular pressure. For example, following 4 to 6 weeks of topical corticosteroid administration, 5% of subjects can show an elevation in intraocular pressure of >16 mmHg and 30% of subjects may be show an elevation of 6 to 15 mmHg (Armaly M., Statistical attributes of the steroid hypertensive response in the clinically normal eye, Invest Ophthalmol V is Sci 1965; 4:187-197; Becker B., Intraocular pressure response to topical corticosteroid, Invest Ophthalmol V is Sci 1965; 4:198-205). Additionally, intravitreal administration of known formulations of a corticosteroid, such as triamcinolone can also result in increased intraocular pressure (Martidis A. et al., Intravitreal triamcinolone for refractory diabetic macular edema, Ophthalmology 2002; 109:920-927; Jonas J. et al., Intravitreal injection of triamcinolone for diffuse diabetic macular edema, Arch Ophthalmol 2003; 121:57-61), possibly due to the burst or high release rates of triamcinolone from the known formulations.

As well as causing an increase in intraocular pressure, corticosteroids can also cause an increase in cataract formation. Corticosteroid-induced cataracts typically show an axial, posterior subcapsular opacity, which gradually increases in size. Nuclear sclerosis is not a typical lens change from corticosteroids. Topical, systemic and peribulbar corticosteroid administration have all been associated with an increased risk of cataract formation (Butcher J. et al., Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. BMJ 1994; 309-343).

The intravitreal administration of known triamcinolone formulations can therefore also be expected to be associated with an increased risk of both elevated intraocular pressure and cataract formation.

A further adverse effect from ocular corticosteroid administration can be inflammation. Endophthalmitis is a type of intraocular inflammation that can be due to infection with pathogens such as bacteria or fungi or can be noninfectious. Clinical features include lid edema, conjunctival injection, corneal edema, anterior chamber and vitreous inflammation and hypotony. Infectious endophthalmitis can occur following an intraocular procedure (i.e. cataract surgery, vitrectomy surgery, intravitreal injection), as a result of systemic infection, as a result of trauma, or occur as a late feature of conjunctival filtering blebs.

The most common dose of triamcinolone used to treat eyes with macular edema associated with diabetes, CRVO or BRVO is 4 mg (Martidis A. et al., Intravitreal triamcinolone for refractory diabetic macular edema, Ophthalmology 2002; 109:920-927). The use of 25 mg of triamcinolone has less commonly been used to treat eyes with macular edema (Jonas J. et al., Intravitreal injection of

[0027] Thus, there are significant drawbacks and deficiencies with the known triamcinolone formulations used by intravitreal administration to treat an ocular condition, including for example rapid clearance from the vitreous, elevated intraocular pressure, cataract formation, retinal toxicity, and intraocular inflammation, such as endophthalmitis.

[0028] Hence, a sterile, preservative-free, sustained release triamcinolone preparation is desirable. Additionally, because corticosteroids have known ocular toxicities (as manifested in the occurrence or development of for example elevated IOP, glaucoma and cataract) it is desirable to have a triamcinolone formulation for intracural (i.e. intravitreal) use which does not result in an increased incidence of elevated IOP, glaucoma, cataract formation and/or intraocular inflammation, or which has, subsequent to intracural administration of a triamcinolone formulation, a reduced incidence of elevated IOP, glaucoma, cataract formation and/or intraocular inflammation as compared to currently used or known intraocular (i.e. intravitreal) use triamcinolone.

DRAWINGS

[0029] FIG. 1 is a bar graph of observed angiographic leakage (as assessed on a 1-5 grading scale) on the Y-axis versus time of the observation on the X-axis for three groups of rabbit eyes: rabbit control (untreated) eyes, rabbit eyes intravitreally injected with the 1 mg triamcinolone acetonide gel suspension (TAA<sub>gp</sub>) formulation of Example 8, and rabbit eyes intravitreally injected with the 4 mg TAA<sub>gp</sub> of Example 9. The grading (scale 1-5) of late-phase angiograms from rabbit eyes was measured over a thirty week period after intravitreal injection of either the 1 mg TAA<sub>gp</sub> or 4 mg TAA<sub>gp</sub>. All eyes received intravitreal injection of 500 ng VEGF at each of the time points shown on the X-axis of FIG. 1, and the area under the fluorescence curve (AUC) was calculated for each eye.

[0030] FIG. 2 is a bar graph of observed retinal fluorescence (as area under the curve) on the Y-axis versus time of the observation on the X-axis for the same three groups of rabbit eyes: rabbit control (untreated) eyes, rabbit eyes intravitreally injected with the 1 mg TAA<sub>gp</sub>, and rabbit eyes intravitreally injected with the 4 mg TAA<sub>gp</sub> (as in FIG. 1). Scanning vitreal fluorophotometry measurements of VEGF-induced BRB breakdown in rabbit eyes was measured over the same thirty week period after intravitreal injection of the 1 mg or 4 mg TAA<sub>gp</sub>. As in FIG. 1, all eyes had received intravitreal injection of 500 ng VEGF at the time points shown on the X-axis followed by fluorophotometry 48 hrs later. The area under the fluorescence curve (AUC) was calculated for each eye.

[0031] FIG. 3 is a bar graph of observed retinal blood vessel caliper and tortuosity (grade) on the Y-axis versus time of the observation on the X-axis for the same rabbit control (untreated) eyes, rabbit eyes intravitreally injected with 1 mg TAA<sub>gp</sub> or with 4 mg TAA<sub>gp</sub> (as in FIG. 1). Subjective grading (on a 1-5 scale) of VEGF-induced changes in vessel caliper and tortuosity from fundus images of rabbit eyes was measured over the same thirty week period after intravitreal injection of the 1 or 4 mg TAA<sub>gp</sub>. As in FIG. 1, all eyes received intravitreal injection of 500 ng VEGF at the indicated time points followed by fundus image capture 48 hrs later.

[0032] FIG. 4 is a bar graph of observed anterior chamber fluorescence (as area under the curve) on the Y-axis versus time of the observation on the X-axis for the same rabbit control (untreated) eyes, rabbit eyes intravitreally injected with 1 mg TAA<sub>gp</sub> or with 4 mg TAA<sub>gp</sub> (as in FIG. 1). Scanning ocular fluorophotometry of VEGF-induced blood-aqueous barrier breakdown in rabbit eyes was measured over a thirty week period after intravitreal injection of either 1 or 4 mg TAA<sub>gp</sub>. As in FIG. 1, all eyes received intravitreal injection of 500 ng VEGF at the indicated time points followed by anterior chamber fluorophotometry 48 hrs later. The area under the fluorescence curve (AUC) was calculated for each eye.

[0033] FIG. 5 is a negative image of a photograph of the eye of a rabbit thirty weeks after intravitreal injection of 50 µL of the Example 94 mg TAA<sub>gp</sub> formulation. The photograph was taken with an 11.0 megapixel, digital Zeiss FF450 fundus camera coupled to the Zeiss 481 Visupac image capture and analysis system.

[0034] FIG. 6 is a flow chart which summarizes a preferred manufacturing process for making triamcinolone formulations of Examples 1 to 9.

[0035] FIG. 7 consists of three bar graphs showing the size (diameter) in microns (x-axis) of triamcinolone acetonide particles in three commercial lots of Kenalog-40 vs the frequency of occurrence of the measured particles diameters. Triamcinolone acetonide particle size diameter and distribution was determined by laser light scattering using a Horiba LA 300 instrument.

[0036] FIG. 8 consists of four bar graphs (A, B, C, and D) showing the size (diameter) in microns (x-axis) of triamcinolone acetonide particles in four lots of the Example 9 (8% Trivaris) formulation vs the frequency of occurrence of the measured particles diameters. The line graph in FIGS. 9A to 9D shows the area under the curve for cumulative (%) triamcinolone acetonide particle size (right hand side x axis). Triamcinolone acetonide particle size diameter and distribution was determined by laser light scattering using a Horiba LA 300 instrument.

SUMMARY

[0037] The present invention provides sterile, preservative-free, sustained release triamcinolone formulations for treating ocular conditions with the desirable characteristics of low ocular toxicities, as manifested in the low or nominal occurrence or development of an elevated IOP, glaucoma, cataract and/or intraocular inflammation.

[0038] Definitions

[0039] As used herein, the words or terms set forth below have the following definitions.

[0040] “About” means that the item, parameter or term so qualified encompasses a range of plus or minus ten percent above and below the value of the stated item, parameter or term.

[0041] “Administration”, or “to administer” means the step of giving (i.e. administering) a pharmaceutical compo-
position to a subject. The pharmaceutical compositions disclosed herein can be “locally administered”, that is administered at or in the vicinity of the site at which a therapeutic result or outcome is desired. For example to treat an ocular condition (such as for example a macular edema, uveitis or macular degeneration) intravitreal injection or implantation of a sustained release device such as active agent containing polymeric implant can be carried out. “Sustained release” means release of an active agent (such as a triamcinolone) over a period of about seven days or more, while “extended release” means release of an active agent over a period of time of less than about seven days.

[0042] “Entirely free (i.e. "consisting of") terminology means that within the detection range of the instrument or process being used, the substance cannot be detected or its presence cannot be confirmed.

[0043] “Essentially free” (or “consisting essentially of”) means that only trace amounts of the substance can be detected.

[0044] “Pharmaceutical composition” means a formulation in which an active ingredient (the active agent) can be a steroid, such as a corticosteroid, such as a triamcinolone. The word “formulation” means that there is at least one additional ingredient in the pharmaceutical composition besides the steroid active ingredient. A pharmaceutical composition is therefore a formulation which is suitable for diagnostic or therapeutic administration (i.e. by intraocular injection or by insertion of a depot or implant) to a subject, such as a human patient.

[0045] “Substantially free” means present at a level of less than one percent by weight of the pharmaceutical composition.

[0046] All the viscosity values set forth herein were determined at 25°C. (unless another temperature is specified). Additionally, all the viscosity values set forth herein were determined at a shear rate of about 0.1/second (unless another shear rate is specified).

[0047] The present compositions are highly suitable for intravitreal administration into the posterior segments of eyes without requiring any washing step, while providing for reduced ocular, for example, retinal, damage when used in an eye. The present compositions are advantageously substantially free of added preservative components, for example, contain no benzyl alcohol preservative. In addition, the present compositions advantageously require no resuspension aid or aids. Overall, the present compositions are easily and effectively injectable into the posterior segment of an eye of a human or animal and can be maintained as a substantially uniform suspension for long periods of time, for example, at least about one week or more, without resuspension processing, for example, without requiring shaking or other agitation of the composition to obtain substantial suspension uniformity. In short, is the present compositions and methods provide substantial enhancements and advantages, for example, relative to the prior art Kenalog® 40 composition and methods of using such prior art composition, in the posterior segments of human or animal eyes.

[0048] In one broad aspect of the present invention, compositions useful for injection into a posterior segment of an eye of a human or animal are provided. Such compositions comprise a corticosteroid component, a viscosity inducing component, and an aqueous carrier component. The corticosteroid component is present in a therapeutically effective amount. The corticosteroid component is present in the compositions in a plurality of particles.

[0049] The present compositions may include a corticosteroid component in an amount of up to about 25% (w/v) or more of the composition. In one very useful embodiment, the corticosteroid component is present in an amount of at least about 80 mg/ml of composition. Preferably, the corticosteroid component is present in an amount in a range of about 1% to about 10% or about 20% (w/v) of the composition.

[0050] In one very useful embodiment, the corticosteroid component comprises triamcinolone acetonide. The viscosity inducing component is present in an amount effective in increasing the viscosity of the composition. Any suitable, preferably ophthalmically acceptable, viscosity inducing component may be employed in accordance with the present invention. Many such viscosity inducing components have been proposed and/or used in ophthalmic compositions used on or in the eye. Advantageously, the viscosity inducing component is present in an amount in a range of about 0.5% to about 20% (w/v) of the composition. In one particularly useful embodiment, the viscosity inducing component is a hyaluronic acid polymer component, such as sodium hyaluronate.

[0051] In one embodiment, the present compositions have a viscosity of at least about 10 cps or at least about 100 cps, preferably at least about 1,000 cps, more preferably at least about 10,000 cps and still more preferably at least about 70,000 cps, for example, up to about 250,000 cps, or about 300,000 cps, at a shear rate of 0.1/second. The present compositions are structured or have make-ups so as to be effectively, for example, manually, injected into a posterior segment of an eye of a human or animal, preferably through a 27 gauge needle, more preferably through a 29 or 30 gauge needle.

[0052] Without wishing to limit the invention to any particular theory of operation, it is believed that the use of relatively high viscosity compositions, as described herein, provides for effective, and preferably substantially uniform, suspension of the steroid component particles while, at the same time, being injectable into the posterior segment of an eye through conventionally, or even smaller than conventionally, used needles.

[0053] In one embodiment of the invention, the corticosteroid component is present in a plurality of particles which are substantially uniformly suspended in the composition and remain substantially uniformly suspended in the composition for at least about 1 week, preferably at least about 2 weeks or at least about 1 month, and still more preferably at least about 6 months or at least about 1 year or at least about 2 years, without requiring resuspension processing, that is, without requiring being shaken or otherwise agitated to maintain the corticosteroid component particles substantially uniformly suspended in the composition.

[0054] Compositions having such substantially uniform suspension of corticosteroid component particles, so as to be able to provide a consistent and accurate dose upon administration to an eye, provide substantial advantages relative to
the prior art. In particular, the present compositions may be manufactured, shipped and stored for substantial periods of time without the corticosteroid component particles precipitating from the remainder of the composition. Having the corticosteroid component particles maintained substantially uniformly suspended in the composition allows the composition to provide long term dosing consistency and accuracy per unit dose amount administered, without any need to resuspend the corticosteroid particles.

[0055] The aqueous carrier component is advantageously ophthalmically acceptable and may include one or more conventional expedients useful in ophthalmic compositions. For example, the carrier component may include an effective amount of at least one of a preservative component, a toxicity component and a buffer component. In one advantageous embodiment, the present compositions include no added preservative component. This feature reduces or minimizes or even substantially eliminates adverse reactions in the eye which may be caused by or linked to the presence of a preservative component. Although a suspension component may be employed in accordance with the present invention, in many instances, because of the ability of the present composition to remain a substantially uniform suspension for a long period of time without requiring resuspension processing, the compositions advantageously contain no added suspension components.

[0056] Methods of treating posterior segments of the eyes of humans or animals are also disclosed and are included within the scope of the present invention. In general, such methods comprise administering, e.g. injecting a corticosteroid component-containing composition, for example, a composition in accordance with the present invention, to a posterior segment of an eye of a human or animal. Such administering is effective in providing a desired therapeutic effect. The administering step advantageously comprises at least one of intravitreal injecting, subconjunctival injecting, sub-tenon injecting, retrobulbar injecting, suprachoroidal injecting and the like.

[0057] Our invention encompasses a pharmaceutical composition for treating a posterior ocular condition. The composition can comprise a triamcinolone present in a therapeutically effective amount as a plurality of particles; a viscosity inducing component in an amount effective to increase the viscosity of the composition, and an aqueous carrier component. The composition can have a viscosity of at least about 10 cps at a shear rate of about 0.1/second and is injectable into the vitreous of a human eye, for example through a 27 gauge needle. By reducing the viscosity of our formulation it can be injected into the vitreous through a 28, 29 or 30 gauge needle.

[0058] Preferably, the triamcinolone particles of the pharmaceutical composition are substantially uniformly suspended in the composition and the viscosity inducing component is a polymeric hyaluronate.

[0059] A detailed embodiment within the scope of our invention is a pharmaceutical composition for treating a posterior ocular condition, comprising triamcinolone particles; polymeric hyaluronate, in which the triamcinolone particles are suspended; sodium chloride; sodium phosphate, and water. The pharmaceutical composition can have a viscosity at a shear rate of about 0.1/second of between about 80,000 cps to about 300,000, preferably from about 128,000 cps to about 225,000 cps. Note that the pharmaceutical composition can have a viscosity at a shear rate of about 0.1/second of between about 80,000 cps and about 300,000 cps, and that when the pharmaceutical composition has a viscosity at a shear rate of about 0.1/second of between about 100,000 cps and about 150,000 cps it can be injected into the vitreous through a 27, 28, 29 or 30 gauge needle. We have found that even with a 300,000 cps our formulations can be injected through a 30 gauge needle due to shear thinning once the formulation is in movement in the syringe. The sodium phosphate present in the pharmaceutical composition can comprise both monobasic sodium phosphate and dibasic sodium phosphate. Additionally, the pharmaceutical composition can comprise between about 2% w/v triamcinolone and about 8% w/v triamcinolone, between about 2% w/v hyaluronate and about 3% w/v hyaluronate, about 0.6% w/v sodium chloride and about 0.03% w/v sodium phosphate to about 0.04% w/v sodium phosphate. Alternately, the pharmaceutical composition of claim 5 can comprise between about is 0.5% w/v hyaluronate and about 6% w/v hyaluronate. If desired the hyaluronate can be heated (see Example 15) to decrease its molecular weight (and therefore its viscosity) in the formulation.

[0060] The pharmaceutical composition can also comprises between about 0.6% w/v sodium chloride to about 0.9% w/v sodium chloride. Generally, more sodium chloride is used in the formulation as less phosphate is used in the formulation, for example 0.9% sodium chloride can be used if no phosphate is present in the formulation, as in this manner the toxicity of the formulation can be adjusted to obtain the desired isotonicity with physiological fluid. The pharmaceutical composition can comprise between about 0.0% w/v sodium phosphate and 0.1% w/v sodium phosphate. As noted, more phosphate can be used in the formulation if less sodium chloride is present in the formulation so as to obtain a desired pH 7.4 buffering effect.

[0061] A more detailed embodiment within the scope of our invention is a pharmaceutical composition for treating a posterior ocular condition, the pharmaceutical composition consisting essentially of triamcinolone particles, polymeric hyaluronate, in which polymeric hyaluronate the triamcinolone particles are suspended, sodium chloride, sodium phosphate, and water. The pharmaceutical composition can have a viscosity at a shear rate 0.1/second at 25°C of between about 128,000 cps and about 225,000 cps and the sodium phosphate present in the pharmaceutical composition can be present as both monobasic sodium phosphate and dibasic sodium phosphate. The most preferable viscosity range is 140,000 to 280,000 cps at a shear rate 0.1/second at 25°C.

[0062] A further embodiment of our invention is a triamcinolone suspension for treating a posterior ocular condition, consisting of triamcinolone particles, polymeric hyaluronate, in which the triamcinolone particles are suspended, sodium chloride, dibasic sodium phosphate heptahydrate, monobasic sodium phosphate monohydrate, and water, wherein the composition has a viscosity at a shear rate 0.1/second of between about is 128,000 cps and about 225,000 cps.

[0063] Our invention also includes a method for treating a posterior ocular condition by administering (as by injecting)
the pharmaceutical composition of claim 1 to the vitreous of a human or animal, thereby treating the posterior ocular condition. Thus we have invented a method for treating macula edema by administering to the vitreous of a human eye a pharmaceutical composition comprising a triamcinolone, and a hyaluronate, wherein the pharmaceutical composition having a viscosity at a shear rate of 0.1/second of between about 128,000 cps and about 225,000 cps.

[0064] A pharmaceutical composition within the scope of our invention for treating a posterior ocular condition can comprise a triamcinolone present in a therapeutically effective amount as a plurality of particles, a viscosity inducing component in an amount effective to increase the viscosity of the composition, and an aqueous carrier component, wherein the composition has a viscosity of at least about 10 cps at a shear rate of 0.1/second and is injectable into the vitreous of a human eye and wherein the pharmaceutical composition releases the triamcinolone with substantially first order release kinetics over a period of at least about 45 days after the intravitreal injection. This pharmaceutical composition can exhibit reduced generation of intraocular inflammation, no plume effect (that is no wide dispersion of the triamcinolone into the vitreous as soon as the triamcinolone is intravitreally injected), and cohesiveness (as shown by the retention of the form of the triamcinolone gel for 30 weeks or longer after intravitreal injection of the triamcinolone gel formulation) upon intravitreal injection of the pharmaceutical composition.

[0065] Our invention encompasses a method for treating a posterior ocular condition, the method comprising the step of intravitreal administration of a sustained release pharmaceutical composition implant comprisin a triamcinolone present in a therapeutically effective amount as a plurality of particles, a viscosity inducing component in an amount effective to increase the viscosity of the composition, and an aqueous carrier component, wherein the composition has a viscosity of at least about 10 cps at a shear rate of 0.1/second and is injectable into the vitreous of a human eye, and wherein the posterior ocular condition is treated for up to about 30 weeks by the triamcinolone released from the implant. In this method the pharmaceutical composition can comprise triamcinolone particles, polymeric hyaluronate, in which the triamcinolone particles are suspended, sodium chloride, sodium phosphate, and water. Additionally, the intravitreal administration can be injected through a 27 gauge needle into the vitreous of a human eye, and in an aggregate number of patients practise of the method results in less intraocular inflammation than does practise of the same method with a second pharmaceutical composition which is a saline solution or suspension of a triamcinolone.

[0066] Our invention also includes a process for making a pharmaceutical composition by (a) mixing triamcinolone particles about 4 microns to about 8 microns in diameter with sodium chloride crystals, and about 35% to about 40% of the total volume of the water (water for injection) used to make the formulation; (b) heating the triamcinolone and sodium chloride mixture to a temperature between about 120° C. and about 140° C., thereby preparing a first part; (c) mixing a sodium phosphate and water, thereby preparing a second part; (d) dissolving sodium hyaluronate with a molecular weight between about 1.0 million Daltons and about 1.9 million Daltons in another about 35% to about 40% of the total water volume used to make the formulation, followed by sterile filtration after the dissolving; (e) lyophilization of the dissolved sodium hyaluronate; (f) reconstitution of the lyophilized, sterile sodium hyaluronate, thereby preparing a third part; and; (g) sceptically combining the first, second and third parts, thereby making a sterile, uniform triamcinolone pharmaceutical composition which is, an opaque white gel suspension suitable for intravitreal injection to treat an ocular condition. Water is added as needed (q.s.) to make the desired gel suspension which is about 80% to about 90% by weight water.

[0067] Also within the scope of our invention is a pharmaceutical composition for treating a posterior ocular condition, the pharmaceutical composition comprising a plurality of corticosteroid particles mixed with a viscous polymer, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25° C., and the pharmaceutical composition can be injected into the vitreous of a human eye through a 25 to 33 gauge needle. The corticosteroid particles can have a substantially uniform diameter, as shown for example by FG85, 8B, 8C and 8D. Additionally, preferably substantially all (i.e. up to 90-97%) of the corticosteroid particles are embedded within the viscous polymer. The corticosteroid can be a triamcinolone and the viscous polymer can be a polymeric hyaluronate or a polymeric hyaluronic acid.

[0068] An alternate method for treating a posterior ocular condition can comprise the step of injecting into the vitreous of a patient's eye with a posterior ocular condition a viscous pharmaceutical composition comprising a plurality of corticosteroid particles mixed into a viscous polymeric matrix, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25° C., such that about one hour after the intravitreal injection only about 10% or less (or only about 5% or less or only about 3% or less) of the corticosteroid particles are present in the viscous free of the polymeric matrix.

[0069] An alternate process for making an intravascular pharmaceutical composition can comprise the step of mixing an aqueous suspension of a plurality of corticosteroid particles and an aqueous solution of a viscous polymeric matrix, so that the resulting pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25° C. The corticosteroid particles can have a median particle size of between about 4 microns and about 5 microns. By use of this process for making an intraocular pharmaceutical composition the corticosteroid particles can have a stable diameter for at least three months after the pharmaceutical has been made and stored for three months in a syringe placed horizontally at about 25° C. at about 60% relative humidity.

[0070] Our invention also includes a pharmaceutical composition for treating an articular pathology, the pharmaceutical composition comprising a plurality of corticosteroid particles mixed with a viscous polymer, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25° C.

[0071] Finally, our invention also includes a method for treating an articular pathology, the method comprising the step of injecting into a joint of a patient with an articular
pathology (such as a joint or spine inflammation) a viscous pharmaceutical composition comprising a plurality of corticosteroid particles mixed into a viscous polymeric matrix, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25° C.

Description

[0072] The present invention is based upon our discovery of triamcinolone formulations specifically designed for intravitreal injection to treat various ocular conditions, such as macula edema. Our triamcinolone formulations have numerous superior characteristics and advantages, including the following: (1) the triamcinolone present in our formulations does not readily settle out from or precipitate from the formulations. Importantly our formulations have a shelf life of at least two years, meaning that our formulations can be left standing for up to about two years before administration to an eye, and after two years the formulation can still provide a consistent and accurate dose of triamcinolone upon injection to the formulation to an eye; (2) our formulations are free of preservatives and resuspension aids, such as benzyl alcohol and/or a polysorbate; (3) concomitantly, our formulations have a much reduced retinal and photoreceptor toxicity; (4) as well as being sterile and preservative-free our triamcinolone formulations can provide sustained release of therapeutic amounts of the triamcinolone over multi-month periods upon intravitreal injection of such formulations. Thus, our viscous suspension triamcinolone formulations can be characterized as sustained release implants; (5) intravitreal administration of our triamcinolone formulations is not associated with an increased incidence of adverse events such as elevated intraocular pressure, glaucoma, cataract and/or intraocular inflammation; (6) intravitreal administration of our triamcinolone formulations is not associated with an increased incidence of adverse events such elevated intraocular pressure, glaucoma, cataract and/or intraocular inflammation as compared to currently used or known intraocular (i.e. intravitreal) use triamcinolone formulations; (7) our formulations permit triamcinolone particles (crystals) to be released (as they solubilize in the viscous fluid of the posterior chamber) from a discrete unitary location, thereby avoiding the plume effect (rapid dispersion) characteristic of aqueous triamcinolone formulations upon intravitreal administration; (8) avoidance of plume formation or rapid dispersion upon intravitreal administration beneficially reduces visual field obscuration; (9) the sustained release characteristic of our formulations reduces the need for intravitreal administration of large drug quantities to achieve a desired therapeutic effect; (10) upon intravitreal administration, the triamcinolone present in our formulations can preferentially be eliminated in posterior direction (that is through the retina and optic nerve) as opposed to elimination through an anterior route (see eg Table 5). This can result in superior treatment of a retinal disease with for example reduced ocular hypertension.

[0073] Advantage (1) above can be provided by formulating the triamcinolone as a viscous, gel suspension, as opposed to formulating it as an aqueous or saline based formulation. Additionally, advantages (4) and (8) above can be provided by particular characteristics of our formulations, such as suspension of the triamcinolone in one or more particular high molecular weight hydrogel polymers which permit sustained release of the triamcinolone from a biocompatible, biodegradable polymeric matrix, and other implant-like characteristics to the formulations, including substantially zero-order in vivo (i.e. intravitreal) release kinetics (see eg Table 4).

[0074] The pluming effect occurs when a saline suspension of a triamcinolone (such as Kenalog) is injected into the vitreous. Pluming prevents visualization of the back of the eye (i.e. the retina is obscured) and also reduces the patient’s visual field (reduced vision).

[0075] Generally, the present invention provides compositions useful for placement, preferably by injection, into a posterior segment of an eye of a human or animal. Such compositions in the posterior, e.g., vitreous, of the eye are therapeutically effective against one or more conditions and/or diseases of the posterior of the eye, and/or one or more symptoms of such conditions and/or diseases of the posterior of the eye.

[0076] It is important to note that while preferably the compositions disclosed herein are preferably administered by intravitreal injection to treat a posterior ocular condition, our compositions (i.e. those of Examples 8 and 9) can also be administered (as by injection) by other routes, such as for example subconjunctival, sub-tenon, periocular, retrobulbar, suprachoroidal, and/or intrascleral to effectively treat an ocular condition. Additionally, a sutured on refillable dome can be placed over the administration site to prevent or to reduce wash out, leaching and/or diffusion of the active agent in a non-preferred direction.

[0077] Compositions within the scope of our invention can comprise a corticosteroid component; a viscosity inducing component; and an aqueous carrier component. The compositions are advantageously ophthalmically acceptable. One of the important advantages of the present compositions is that they are more compatible with or friendly to the tissues in the posterior segment of the eye, for example, the retina of the eye, relative to compositions previously proposed for intravitreal injection into a posterior segment of an eye, for example, a composition sold under the trademark Kenalog®-40. In particular, the present compositions advantageously are substantially free of added preservative components or include effective preservative components which are more compatible with or friendly to the posterior segment, e.g., is retina, of the eye relative to benzyl alcohol, which is included in the Kenalog®-40 composition as a preservative.

[0078] In addition, the present compositions preferably include no added resuspension component, such as polysorbate-80, which is included in the Kenalog®-40 composition. Many of the other features of the present compositions, as described elsewhere herein, also render the present compositions more compatible with or friendly to the posterior segments of the eyes into which the compositions are placed relative to prior art compositions, such as Kenalog®-40.

[0079] As noted above, the present compositions include a corticosteroid component. Such corticosteroid component is present in the compositions in a therapeutically effective amount, that is in an amount effective in providing a desired therapeutic effect in the eye into which the composition is placed. The corticosteroid component is present in the composition in a plurality of particles. Any suitable corticosteroid component may be employed in accordance with the
present invention. Such corticosteroid component advantageously has a limited solubility in water, for example, at 25°C. For example, the corticosteroid component preferably has a solubility in water at 25°C of less than 10 mg/ml. Of course, the corticosteroid component should be ophthalmically acceptable, that is, should have substantially no significant or undue detrimental effect of the eye structures or tissues. One particularly useful characteristic of the presently useful corticosteroid components is the ability of such component to reduce inflammation in the posterior segment of the eye into which the composition is placed caused by the result of one or more diseases and/or conditions in the posterior segment of the eye.

[0080] Examples of useful corticosteroid components include, without limitation, cortisone, prednesolone, triamcinolone, triamcinolone acetonide, fluocinolone acetonide, deflazacort, prednicarbate, budesonide, halobetasol, derivatives thereof and mixtures thereof. As is used herein, the term “derivative” refers to any substance which is sufficiently structurally similar to the material of which it is identified as a derivative so as to have substantially similar functionality or activity, for example, therapeutic effectiveness, as the material when the substance is used in place of the material. In one very useful embodiment, the corticosteroid component comprises triamcinolone acetonide.

[0081] The corticosteroid component advantageously is present in an amount of at least about 10 mg per ml of the composition. One important advantage of the present invention is the effective ability of the present compositions to include relatively large amounts or concentrations of the corticosteroid component. Thus, the corticosteroid component may be present in the present compositions in an amount in the range of about 1% or less to about 5% or about 10% or about 20% or about 30% or more (w/v) of the composition. Providing relatively high concentrations or amounts of corticosteroid component in the present compositions is beneficial in that reduced amounts (volumes for injection) of the composition may be required to be placed or injected into the posterior segment of the eye in order to provide the same amount or more corticosteroid component in the posterior segment of the eye relative to compositions, such as Kenalog®-40, which include less than 4% (w/v) of the corticosteroid component. Thus, in one very useful embodiment, the present compositions include more than about 4% (w/v), for example at least about 5% (w/v), to about 10% (w/v) or about 20% (w/v) or about 30% (w/v) of the corticosteroid component. For example, about 50 μl of our Example 8 or 9 formulation provide respectively 2 mg and 4 mg of triamcinolone. This is in contrast to other formulations (such as Kenalog 40) which require 100 μl to provide 4 mg of triamcinolone. Injection of 100 μl or more of a fluid into the vitreous can result in an excess of fluid in the vitreous with elevated intraocular pressure and leakage of the fluid from the vitreous then potentially occurring.

[0082] The viscosity inducing component is present in an effective amount in increasing, advantageously substantially increasing, the viscosity of the composition. Without being limited to or construing to any particular theory of operation, it is believed that increasing the viscosity of the compositions to values well in excess of the viscosity of water, for example, at least about 100 cps at a shear rate of 0.1/sec, compositions which are highly effective for placement, e.g., injection, into the posterior segment of an eye of a human or animal are obtained. Along with the advantageous placement or injectability of the present compositions into the posterior segment, the relatively high viscosity of the present compositions are believed to enhance the ability of the present compositions to maintain the corticosteroid component particles in substantially uniform suspension in the compositions for prolonged periods of time, for example, for as long as 1 to 2 years, without requiring resuspension processing. The relatively high viscosity of the present compositions may also have an additional benefit of at least assisting the compositions to have the ability to have an increased amount or concentration of the corticosteroid component, as discussed elsewhere herein, for example, while maintaining such corticosteroid component in substantially uniform suspension for prolonged periods of time.

[0083] Advantageously, the present compositions have viscosities of at least about 1000 cps or at least about 1000000000.1 sec, more preferably at least about 1000000000.1 sec or more, for example up to about 1000000000.1 sec or about 1000000000.1 sec or more, at a shear rate of 0.1/sec. The present compositions not only have the relatively high viscosity as noted above but also have the ability or are structured or made up so as to be effectively placeable, e.g., injectable, into a posterior segment of an eye of a human or animal, preferably through a 27 gauge needle, or even through a 30 gauge needle.

[0084] The presently useful viscosity inducing components preferably are shear thinning components in that as the present composition containing such a shear thinning viscosity inducing component is passed or injected into the posterior segment of an eye, for example, through a narrow space, such as 27 gauge needle, under high shear conditions the viscosity of the composition is substantially reduced during such passage. After such passage, the composition regains substantially its pre-injection viscosity so as to maintain the corticosteroid component particles in suspension in the eye.

[0085] Any suitable viscosity inducing component, for example, ophthalmically acceptable viscosity inducing component, may be employed in accordance with the present invention. Many such viscosity inducing components have been proposed and/or used in ophthalmic compositions used on or in the eye. The viscosity inducing component is present in an amount effective in providing the desired viscosity to the composition. Advantageously, the viscosity inducing component is present in an amount in a range of about 0.5% or about 1.0% to about 5% or about 10% or about 20% (w/v) of the composition. The specific amount of the viscosity inducing component employed depends upon a number of factors including, for example and without limitation, the specific viscosity inducing component being employed, the molecular weight of the viscosity inducing component being employed, the viscosity desired for the present composition being produced and/or used and the like factors, such as shear thinning. The viscosity inducing component is chosen to provide at least one advantage, and preferably multiple advantages, to the present compositions, for example, in terms of each of injectability into the posterior segment of the eye, viscosity, sustainability of the corticosteroid component particles in suspension, for example, in substantially uniform suspension, for a pro-
longed period of time without resuspension processing, compatibility with the tissues in the posterior segment of the eye into which the composition is to be placed and the like advantages. More preferably, the selected viscosity inducing component is effective to provide two or more of the above-noted benefits, and still more preferably to provide all of the above-noted benefits.

The viscosity inducing component preferably comprises a polymeric component and/or at least one viscoelastic agent, such as those materials which are useful in ophthalmic surgical procedures.

Examples of useful viscosity inducing components include, but are not limited to, hyaluronic acid (such as a polymeric hyaluronic acid), carbomers, polyacrylic acid, cellulosic derivatives, polycarboxylic acids, polyvinylpyrrolidone, gelatin, dextrin, polysaccharides, polyacrylamide, polyvinyl alcohol, polyvinyl acetate, derivatives thereof and mixtures and copolymers thereof.

The molecular weight of the presently useful viscosity inducing components may be in a range of about 10,000 Daltons or less to about 2 million Daltons or more. In one particularly useful embodiment, the molecular weight of the viscosity inducing component is in a range of about 100,000 Daltons or about 200,000 Daltons to about 1 million Daltons or about 1.5 million Daltons. Again, the molecular weight of the viscosity inducing component useful in accordance with the present invention, may vary over a substantial range based on the type of viscosity inducing component employed, and the desired final viscosity of the present composition in question, as well as, possibly one or more other factors.

In one very useful embodiment, a viscosity inducing component is a polymeric hyaluronic acid component, for example, a metal hyaluronate component, preferably selected from alkali metal hyaluronates, alkaline earth metal hyaluronates and mixtures thereof, and still more preferably selected from sodium hyaluronates, and mixtures thereof. The molecular weight of such hyaluronate component (i.e. a polymeric hyaluronic acid) preferably is in a range of about 50,000 Daltons or about 100,000 Daltons to about 1.3 million Daltons or about 2 million Daltons. In one embodiment, the present compositions include a polymeric hyaluronate component in an amount about 0.05% to about 0.5% (w/v). In a further useful embodiment, the hyaluronate component is present in an amount in a range of about 1% to about 4% (w/v) of the composition. In this latter case, the very high polymer viscosity forms a gel that slows particle sedimentation rate to the extent that often no resuspension processing is necessary over the estimated shelf life, for example, at least about 2 years, of the composition. Such a composition may be marketed in pre-filled syringes since the gel cannot be easily removed by a needle and syringe from a bulk container. Pre-filled syringes have the advantages of convenience for the injector and the safety which results from less handling.

The aqueous carrier component is advantageously ophthalmically acceptable and may include one or more conventional excipients useful in ophthalmic compositions. The present compositions preferably include a major amount of liquid water. The present compositions may be, and are preferably, sterile, for example, prior to being used in the eye.

The present compositions preferably include at least one buffer component in an amount effective to control the pH of the composition and/or at least one tonicity component in an amount effective to control the tonicity or osmolality of the compositions. More preferably, the present compositions include both a buffer component and a tonicity component.

The buffer component and tonicity component may be chosen from those which are conventional and well known in the ophthalmic art. Examples of such buffer components include, but are not limited to, acetate buffers, citrate buffers, phosphate buffers, borate buffers and the like and mixtures thereof. Phosphate buffers are particularly useful. Useful tonicity components include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and other sugar alcohols, and other suitable ophthalmically acceptable tonicity and mixtures thereof.

The amount of buffer component employed preferably is sufficient to maintain pH of the composition in a range of about 6 to about 8, preferably about 7 to 7.5. The amount of tonicity component employed preferably is sufficient to provide an osmolality to the present compositions in a range of about 200 to about 400, more preferably about 250 to about 350, mOsmol/kg respectively. Advantageously, the present compositions are substantially isotonic.

The present compositions may include one or more other components in amounts effective to provide one or more useful properties and/or benefits to the present compositions. For example, although the present compositions may be substantially free of added preservative components, in other embodiments, the present compositions include effective amounts of preservative components, preferably such components which are more compatible with or friendly to the tissue in the posterior segment of the eye into which the composition is placed than benzyl alcohol. Examples of such preservative components include, without limitation, benzalkonium chloride, chlorhexidine, PHMB (polyhexamethylenebiguanide), methyl and ethyl parabens, hexetidine, chloride components, such as stabilized chlorine dioxide, metal chlorites and the like, other ophthalmically acceptable preservatives and the like and mixtures thereof.

The concentration of the preservative component, if any, in the present compositions is a concentration effective to preserve the composition, and is often in a range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition.

In addition, the present composition may include an effective amount of reuspension component effective to facilitate the suspension or resuspension of the corticosteroid component particles in the present compositions. As noted above, in certain embodiments, the present compositions are free of added resuspension components. In other embodiments of the present compositions effective amounts of resuspension components are employed, for example, to provide an added degree of insurance that the corticosteroid component particles remain in suspension, as desired and/or can be relatively easily resuspended in the present compositions, such resuspension being desired. Advantageously, the resuspension component employed in accordance with the present invention, if any, is chosen to be more compatible
with or friendly to the tissue in the posterior segment of the eye into which the composition is placed than polysorbate 80.

[0096] Any suitable resuspension component may be employed in accordance with the present invention. Examples of such resuspension components include, without limitation, surfactants such as poloxanes, for example, sold under the trademark Pluronics®; tyloxapol; sarcosides; polyethoxylated castor oils, other surfactants and the like and mixtures thereof.

[0097] One very useful class of resuspension components are those selected from vitamin derivatives. Although such materials have been previously suggested for use as surfactants in ophthalmic compositions, they have been found to be effective in the present compositions as resuspension components. Examples of useful vitamin derivatives include, without limitation, Vitamin E tocopheryl polyethylene glycol succinates, such as Vitamin E tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS). Other useful vitamin derivatives include, again without limitation, Vitamin E tocopheryl polyethylene glycol succinimides, such as Vitamin E tocopheryl polyethylene glycol 1000 succinimide (Vitamin E TPGSA) wherein the ester bond between polyethylene glycol and succinic acid is replaced by an amide group.

[0098] The presently useful resuspension components are present, if at all, in the compositions in accordance with the present invention in an amount effective to facilitate suspending the particles in the present compositions, for example, during manufacture of the compositions or thereafter. The specific amount of resuspension component employed may vary over a wide range depending, for example, on the specific resuspension component being employed, the specific composition in which the resuspension component is being employed and the like factors. Suitable concentrations of the resuspension component, if any, in the present compositions are often in a range of about 0.01% to about 5%, for example, about 0.02% or about 0.05% to about 1.0% (w/v) of the composition.

[0099] The availability of minimally soluble corticosteroid, such as triamcinolone acetonide, to intraocular tissues may be limited by the dissolution rate for these substances. Slow dissolution is both good and bad for the patient. On the one hand, after a single intravitreal injection of the present composition, the mean elimination half-life for triamcinolone acetonide is disadvantageously quite long, for example, about 19 days in nonvitrectomized patients and measurable drug levels are detected for up to about 3 months. On the other hand, therapeutic drug levels in the vitreous compartment of the eye may not be achieved for about 1 to about 3 days, due to the slow dissolution rate of the corticosteroid component particles.

[0100] In one embodiment of the present invention, an effective amount of a solubilizing component is provided in the composition to solubilize a minor amount, that is less than 50%, for example in a range of 1% or about 5% to about 10% or about 20% of the corticosteroid component. For example, the inclusion of a cyclodextrin component, such as β-cyclodextrin, sulfobutyl ether β-cyclodextrin (SBE), other cyclodextrins and the like and mixtures thereof, at about 0.5 to about 5.0% (w/v) solubilizes about 1 to about 10% of the initial dose of triamcinolone acetonide. This presolubilized fraction provides a readily bioavailable loading dose, thereby avoiding any delay time in therapeutic effectiveness.

[0101] The use of such a solubilizing component is advantageous to provide any relatively quick release of the corticosteroid component into the eye for therapeutic effectiveness. Such solubilizing component, of course, should be ophthalmically acceptable or at least sufficiently compatible with the posterior segment of the eye into which the composition is placed to avoid undue damage to the tissue in such posterior segment.

[0102] The pharmacokinetics of the corticosteroid component, for example, triamcinolone acetonide, following intravitreal administration may involve both the rate of drug dissolution and the rate of drug efflux via the anterior route. For example, following a single intravitreal injection of a composition containing 4% (w/v) of triamcinolone acetonide, triamcinolone acetonide concentration peaks (monitored in aqueous humor) after several days at thousands of nanograms per ml. This peak (C_max) is followed by a rapid decrease lasting about 200 hours, and ends in a slow elimination phase with a half-life of about 19 days. Patients typically require repeat dosing, for example about every three months.

[0103] In one embodiment of the present invention, the compositions further contain sustained release components, for example, polymers (in the form for example of gels and microspheres), such as poly (D,L-lactide) or poly(D,L-lactide co-glycolide), in amounts effective to reduce local diffusion rates and/or corticosteroid particle dissolution rates. The result is a flatter elimination rate profile with a lower C_max and a more prolonged therapeutic window, thereby extending the time between required injections for many patients.

[0104] Any suitable, preferably conditionally acceptable, release component may be employed. Useful examples are set forth above. The sustained release component is preferably biodegradable or bioabsorbable in the eye so that no residue remains over the long term. The amount of the delayed release component included may vary over a relatively wide range depending, for example, on the specific sustained release component is being employed, the specific release profile desired and the like factors. Typical amounts of delayed release components, if any, included in the present compositions are in a range of about 0.05 to 0.1 to about 0.5 or about 1 or more percent (w/v) (weight of the ingredient in the total volume of the composition) of the composition.

[0105] The present compositions can be prepared using suitable blending/processing techniques or techniques, for example, one or more conventional blending techniques. The preparation processing should be chosen to provide the present compositions in forms which are useful for placement or injection into the posterior segments of eyes of humans or animals. In one useful embodiment a concentration corticosteroid component dispersion is made by combining the corticosteroid component with water, and the excipient (other than the viscosity inducing component) to be included in the final composition. The ingredients are mixed to disperse the corticosteroid component and then autoclaved. Alternatively, the steroid powder may be γ-irradiated before addition to the sterile carrier. The viscosity inducing component may be purchased sterile or sterilized.
Methods of using the present composition are provided and are included within the scope of the present invention. In general, such methods comprise administering a composition in accordance with the present invention to a posterior segment of an eye of a human or animal, thereby obtaining desired therapeutic effect. The administering step advantageously comprises at least one of intravitreal injecting, subconjunctival injecting, subtenon injecting, retrolubar injecting, suprachoroidal injecting and the like. A syringe apparatus, including appropriately sized needle for example, for a 27 gauge needle or a 30 gauge needle, can be effectively used to inject the composition within the posterior segment of an eye of a human or animal.

Ocular conditions which can be treated or addressed in accordance with the present invention include, without limitation, the following:

Maculopathies/retinal degeneration: macular degeneration, including age related macular degeneration (ARMD), such as non-exudative age related macular degeneration and exudative age related macular degeneration, choroidal neovascularization, retinopathy, including diabetic retinopathy, acute and chronic macular neuroretinopathy, central serous choroidopathy, and macular edema, including cystoid macular edema, and diabetic macular edema. Uveitis/retinitis/choroiditis: acute multifocal placoid pigment epitheliopathy, Behçet’s disease, birdshot retinochoroidopathy, infectious (syphilis, Lyme, tuberculosis, toxoplasmosis), uveitis, including intermediate uveitis (pars planitis) and anterior uveitis, multifocal choroiditis, multiple evanescent white dot syndrome (MEWDS), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis, uveitis syndrome, and Vogt-Koyanagi-Harada syndrome. Vascular diseases/exudative diseases: retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coats’ disease, paradoxic telangiectasis, hemiretinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angiod streaks, familial exudative vitreoretinopathy, Eales disease. Traumatic/surgical: sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, laser, PDT, photocoagulation, hyperperfusion during surgery, radiation retinopathy, bone marrow transplant retinopathy. Proliferative disorders: proliferative vitreal retinopathy and epiretinal membranes, proliferative diabetic retinopathy. Infectious disorders: ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associated with HIV infection, uveitic disease associated with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis. Genetic disorders: retinitis pigmentosa, systemic disorders with associated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt’s disease and fundus flavimaculatus, Best’s disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby’s is fundus dystrophy, benign concentric maculopathy, Bietti’s crystalline dystrophy, pseudoexfoliation elastica. Retinal tears/holes: retinal detachment, macular hole, giant retinal tear. Tumors: retinal disease associated with tumors, congenital hypertrophy of the RPE, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma, intraocular lymphoid tumors. Miscellaneous: punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, acute retinal pigment epitheliopathy and the like.

The present methods may comprise a single injection into the posterior segment of an eye or may involve repeated injections, for example over periods of time ranging from about one week or about one month or about 3 months to about 6 months or about 1 year or longer.

EXAMPLES

The following non-limiting Examples are presented to exemplify aspects of the present invention.

Examples 1 to 4

Four compositions are as follows:

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
</tr>
<tr>
<td>Sodium Hyaluronate</td>
</tr>
<tr>
<td>(0.6 x 10^6 DALTONS)</td>
</tr>
<tr>
<td>Sodium Phosphate</td>
</tr>
<tr>
<td>Vitamin E-TPGS</td>
</tr>
<tr>
<td>γ-cyclodextrin</td>
</tr>
<tr>
<td>Water for Injection</td>
</tr>
<tr>
<td>Viscosity at shear rate</td>
</tr>
<tr>
<td>0.1/second</td>
</tr>
</tbody>
</table>

Each of these compositions is prepared as follows.

A concentrated triamcinolone acetonide dispersion is made by combining triamcinolone acetonide with water, Vitamin E-TPGS and γ-cyclodextrin, if any. These ingredients are mixed to disperse the triamcinolone acetonide, and then autoclaved. The sodium hyaluronate may be purchased as a sterile powder or sterilized by filtering a dilute solution followed by lyophilization to yield a sterile powder. The sterile sodium hyaluronate is dissolved in water to make an aqueous concentrate. The concentrated triamcinolone acetonide dispersion is mixed and added as a slurry to the sodium hyaluronate concentrate. Water is added q.s. (quantum sufficient, as much as suffices, in this case as much as is...
required to prepare the homogenous mixture, dispersion, gel or suspension) and the mixture is mixed until homogenous.

[0114] Each of these compositions produced a loose floculation of triamcinolone acetonide that is easily re-suspended by gentle inversion. These compositions can be marketed in small volume pharmaceutical grade glass bottles, and are found to be therapeutically effective against macular edema when injected intravitreally into human eyes.

Examples 5 to 7

[0115] Three compositions are as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Example 5</th>
<th>Example 6</th>
<th>Example 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for Injection</td>
<td>0.4% (w/v)</td>
<td>0.4% (w/v)</td>
<td>0.4% (w/v)</td>
</tr>
<tr>
<td>Sodium phosphate, monohydrate</td>
<td>0.04% (w/v)</td>
<td>0.04% (w/v)</td>
<td>0.04% (w/v)</td>
</tr>
<tr>
<td>Viscosity at shear rate 0.1/second</td>
<td>180,000 cps</td>
<td>100,000 cps</td>
<td>100,000 cps</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Example 8</th>
<th>Example 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium hyaluronate (polymeric)</td>
<td>2.5% (w/v)</td>
<td>2.5% (w/v)</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0.63% (w/v)</td>
<td>0.63% (w/v)</td>
</tr>
<tr>
<td>Dibasic sodium phosphate, heptahydrate</td>
<td>0.30% (w/v)</td>
<td>0.30% (w/v)</td>
</tr>
<tr>
<td>Viscosity at shear rate 0.1/second</td>
<td>200,000 cps</td>
<td>25% cps</td>
</tr>
</tbody>
</table>

[0116] These compositions are prepared in a manner substantially analogous to that set forth in Example 1.

[0117] The high viscosities of the compositions substantially slows the particle sedimentation rate to an extent that no resuspension processing is necessary or required over the estimated shelf life, e.g., about 2 years, of the compositions. These compositions can be marketed in prefilled syringes since they can not easily be removed by a needle and syringe from a container. However, with the compositions in prefilled syringes, the compositions can be effectively injected into the posterior segment of an eye of a human using a 27 gauge or a 30 gauge needle to provide a desired therapeutic effect in the human eye.

[0118] The compositions of Examples 5 to 7 employ or contain a sufficient concentration of high molecular weight sodium hyaluronate so as to form a gelatinous plug or drug depot upon intravitreal injection into a human eye. Triamcinolone acetonide particles are, in effect, trapped or held within this viscous plug, so that undesirable pluming does not occur, and the risk of drug particles disadvantageously settling directly on the retinal tissue is substantially reduced, for example, relative to using a composition with a water-like viscosity, such as Kenalog® 40. Since sodium hyaluronate solutions are subject to dramatic shear thinning, these formulations are easily injected through 27 gauge or even 30 gauge needles.

Examples 8 and 9

[0119] Two compositions are as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Example 8</th>
<th>Example 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamcinolone acetonide</td>
<td>2.0% (w/v)</td>
<td>8.0% (w/v)</td>
</tr>
<tr>
<td>Sodium hyaluronate (polymeric)</td>
<td>2.5% (w/v)</td>
<td>2.5% (w/v)</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0.63% (w/v)</td>
<td>0.63% (w/v)</td>
</tr>
<tr>
<td>Dibasic sodium phosphate, heptahydrate</td>
<td>0.30% (w/v)</td>
<td>0.30% (w/v)</td>
</tr>
<tr>
<td>Viscosity at shear rate 0.1/second</td>
<td>170,000 cps</td>
<td>25% cps</td>
</tr>
</tbody>
</table>

[0120] These compositions are prepared in a manner substantially analogous to that set forth in Example 1.

[0121] The high viscosities of the compositions substantially slows the particle sedimentation rate to an extent that no resuspension processing is necessary or required over the estimated shelf life, e.g., about 2 years, of the compositions. These compositions can be marketed in prefilled syringes since they can not easily be is removed by a needle and syringe from a container. However, with the compositions in prefilled syringes, the compositions can be effectively injected into the posterior segment of an eye of a human using a 27 gauge or a 30 gauge needle to provide a desired therapeutic effect in the human eye.

[0122] The sodium hyaluronate powders used in these compositions (as well as in the other compositions identified in the Examples herein) have water contents in a range of about 4% to about 20%, preferably about 4% to about 8%, by weight. Differences in the average molecular weight of the hyaluronate used can result in variation in the viscosity of compositions in accordance with the present invention which have the same nominal chemical make-ups. Thus, the viscosities indicated herein should be understood to be target viscosities, with the composition being acceptable for use if the actual viscosity of the composition is within plus or minus (±) about 25% or about 30% or about 35% of the target viscosity.

[0123] Because each of the compositions set forth in the Examples has a density of about 1 gm/ml, the percentages set forth herein as being based on weight per volume (w/v) can also be considered as being based on weight per weight (w/w).

[0124] The compositions of Examples 8 and 9 employ or contain a sufficient concentration of high molecular weight (i.e. polymeric) sodium hyaluronate so as to form a gelatinous plug or drug depot upon intravitreal injection into a human eye. Preferably the average molecular weight of the hyaluronate used is less than about 2 million, and more preferably the average molecular weight of the hyaluronate used is between about 1.3 million and 1.6 million. The triamcinolone acetonide particles are, in effect, trapped or held within this viscous plug of hyaluronate, so that undesirable pluming does not occur upon intravitreal injection of the formulation. Thus, the risk of drug particles disadvantageously settling directly on the retinal tissue is substantially reduced, for example, relative to using a composition with a water-like viscosity, such as Kenalog® 40. Since sodium hyaluronate solutions are subject to dramatic shear thinning, these formulations are easily injected through 27 gauge or even 30 gauge needles.

[0125] The most preferred viscosity range for the Example 8 and 9 formulations is 140,000 cps to 280,000 cps at a shear rate 0.1/second at 25° C.
The triamcinolone acetonide used in the formulations set forth herein has the chemical name 9-Fluoro-11,21-dihydroxy-1,6,17-[1-methyl-ethylenedibis(oxy)]pregna-1,4-diene-3,20-dione, and can have the following structure.

The molecular formula of triamcinolone acetonide is C_{28}H_{30}FO_8 and its molecular weight is 434.49. The solubility of triamcinolone acetonide in water is about 25.4 µM/L.

The Examples 8 and 9 formulations are prepared as sterile products of a uniform, opaque white dispersion of microfine triamcinolone acetonide particles suspended in a hyaluronate-based polymeric hydrogel, intended for intravitreal injection.

The Examples 8 and 9 formulations can be used top treat, for example, macular edema in patients with diabetes, central retinal vein occlusion, and branch retinal vein occlusion. Notable the Examples 8 and 9 formulations are formulated using only excipients that are fully compatible (i.e., non-toxic) to the eye, particularly to the retina. The Examples 8 and 9 formulations (2% w/w) and 8% w/w triamcinolone acetonide, respectively) are buffered at physiological pH with a low concentration of sodium phosphate salts; rendered isotonic with sodium chloride, and use Water for Injection, USP, as the vehicle.

A target dosage of 1 mg of the triamcinolone acetonide active agent can be delivered in a 50 mg (approximately 48 µL) injection of the Example 82% (w/v) triamcinolone acetonide gel suspension formulation. A target dosage of 4 mg of the triamcinolone acetonide active agent can be delivered in a 50 mg (approximately 48 µL) injection of the Example 98% (w/w) triamcinolone acetonide gel suspension formulations.

As noted, the triamcinolone present in our formulations does not rapidly, or even slowly, settle out from or precipitate from the formulations. Significantly our Example 8 and 9 formulations have a shelf life of at least two years, meaning that these formulations can be left standing (without agitation) for up to about two years before administration to an eye, and after two years the same formulations can still provide a consistent and accurate dose of triamcinolone upon injection to the formulation to an eye. For example, upon preparation (as set froth in Example 15), 50 µL of our 8% formulation provides 4 mg of triamcinolone acetonide, and if left standing for up to about 2 years 50 µL of our 8% formulation stills provides 4 mg ± 15% of triamcinolone acetonide, thereby meeting the U.S.P. definition of consistent dosage after storage.

As noted, the composition of triamcinolone 2% injectable gel suspension (Example 8) is triamcinolone 2.0% (w/w), sodium hyaluronate, sodium chloride, dibasic sodium phosphate (heptahydrate), monobasic sodium phosphate (monohydrate), and water for injection. The composition of triamcinolone 8% injectable gel suspension (Example 9) is triamcinolone 8.0% (w/w), sodium hyaluronate, sodium chloride, dibasic sodium phosphate (heptahydrate), monobasic sodium phosphate (monohydrate), and water for injection.

The triamcinolone acetonide injectable gel suspension we have invented is a viscous suspension of triamcinolone acetonide formulated at concentrations of 8% and 2% with sodium hyaluronate, sodium chloride, dibasic sodium phosphate (heptahydrate), monobasic sodium phosphate (monohydrate), and water for injection (i.e. the formulations of Examples 8 and 9 respectively). The suspensions are prepared to have physiologic pH, and to be isotonic, and preservative-free. The Examples 8 and 9 suspensions can be supplied in single-use glass syringes with fixed 27 gauge needles. The syringes are overfilled to 0.17-0.18 mL, and calibrated to deliver 0.05 mL when primed to a black or blue mark on the barrel of the syringe to thereby provide the 2% and 8% suspensions to deliver 1 mg and 4 mg of triamcinolone, respectively (the pre-filled syringes are made by Allergan, Inc., Irvine, Calif.). These syringes have a shelf life of at least about two years when stored at 2-8°C.

Example 10

Ocular and Systemic Pharmacokinetics of a 4% (4 mg) Triamcinolone Acetonide Gel Suspension Formulation upon Intravitreal Injection

An experiment was carried out to evaluate the intraocular and systemic pharmacokinetics of triamcinolone acetonide gel suspensions (TAA_{gel}) following intravitreal administration. The formulations used were: (1) 4% w/v (40 mg/mL) triamcinolone acetonide formulated as a high viscosity borate-buffered 2.5% w/w hyaluronic acid suspension, and; (2) 16% w/v (160 mg/mL) triamcinolone acetonide formulated as a high viscosity borate-buffered 2.5% (w/w). 100 µL of each formulation was injected into separate rabbit eyes using a 25-gauge needle syringe to provide 4 mg or 16 mg of triamcinolone acetinide, respectively. Except as noted the formulations used in this Example 10 were the same as the Example 8 and 9 formulations. For example, the same type of sodium hyaluronate was used in these Example 10 formulations.

Following a single intravitreal injection (New Zealand albino rabbits) of 100 µL of the 4% w/v triamcinolone acetonide formulation (4 mg triamcinolone acetonide), aqueous humor, vitreous humor, retina and plasma were collected on days 1, 3, 10, 17, 31 and 45 and analyzed for triamcinolone acetonide by liquid chromatography tandem mass spectrometry. In vitreous humor, the maximal triamcinolone acetonide concentration (C_{max}) was 385 µg/g on Day 10. The relatively constant concentrations (i.e. sustained release) of triamcinolone acetonide were observed from Day 1 to Day 45. (Tables 4 and 5) Therefore, the TAA_{gel} formulation delivers a relatively stable concentration (i.e. approximately zero-order release kinetics) of triamcinolone acetonide to the retina over at least 45-day period following single intravitreal injection.

Table 4 also shows that the ratio of the amount of triamcinolone acetonide present in the vitreous to the
amount of triamcinolone acetonide present in the aqueous chamber can be greater than 1000:1 at all time points. Table 5 shows that ratio of the total amount of triamcinolone acetonide present in the vitreous over the 45 day study period to the total amount of triamcinolone acetonide present in the aqueous humor over the 45 day study period can be greater than about 5,000:1.

<table>
<thead>
<tr>
<th>Timepoint (Day)</th>
<th>Aqueous Humor</th>
<th>Vitreous Humor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.339</td>
<td>382</td>
</tr>
<tr>
<td>3</td>
<td>0.200</td>
<td>335</td>
</tr>
<tr>
<td>10</td>
<td>0.052</td>
<td>385</td>
</tr>
<tr>
<td>17</td>
<td>0.033</td>
<td>338</td>
</tr>
<tr>
<td>31</td>
<td>0.014</td>
<td>185</td>
</tr>
<tr>
<td>45</td>
<td>0.011</td>
<td>222</td>
</tr>
</tbody>
</table>

Table 4

Pharmacokinetic parameters of triamcinolone acetonide in ocular tissues after a single intravitreal injection of 4% triamcinolone acetonide formulation in albino rabbits.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL or µg/g)</th>
<th>AUC&lt;sub&gt;0-45 day&lt;/sub&gt; (µg · day/mL or µg · day/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous Humor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% Triamcinolone Injectable</td>
<td>385</td>
<td>12500</td>
</tr>
<tr>
<td>Aqueous Humor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% Triamcinolone Injectable</td>
<td>0.319</td>
<td>2.36</td>
</tr>
</tbody>
</table>

Following intravitreal administration of the 4% TAA<sub>aq</sub> formulation in albino rabbits, triamcinolone acetonide was absorbed into the systemic circulation with mean plasma C<sub>max</sub> of 15.8 ng/mL at 1 day postdose. Between days 2 and 45, plasma levels drop to 7 and 1 ng/mL, respectively. Thus, our the triamcinolone acetonide gel suspension formulations are free of excipients with known ocular toxicity, and through sustained release from the gel delivers prolonged levels of triamcinolone acetonide to the vitreous and retina.

Example 11

Triamcinolone Gel Suspensions to Treat Ocular Conditions

Introduction

As set forth herein, we have invented triamcinolone acetonide gel suspensions (TAA<sub>aq</sub>) and their use to treat various ocular conditions, including macular edema, such as macular edema associated with diabetes and/or a retinal vein occlusion, (branch or central), and to maintain or to improve visual acuity. Our TAA<sub>aq</sub> formulations can contain a polymeric hyaluronic acid.

The blood-aqueous barrier ("BAB") is a membrane of the capillary bed of the ciliary body of the eye that influences or controls two-way transfer of fluids between the aqueous chamber of the eye and the blood. The BAB acts as an anatomical mechanism to reduce or prevent exchange of materials between the chambers of the eye and the blood.

The blood-retinal barrier ("BRB") is composed of specialized nonfenestrated tightly-jointed (tight junction) retinal epithelium and adjacent retinal blood vessel endothelium cells that forming a transport barrier for certain substances between the retinal capillaries and the retinal tissue. BRB breakdown is symptomatic of various retinal ocular conditions, including reduced visual acuity, macular edema, macula degeneration, retinal swelling, and other retinopathies, including diabetic retinopathy.

This experiment was designed to assess efficacy and duration of action of particular TAA<sub>aq</sub> polymeric hyaluronic acid formulations injected intravitreally to treat breakdown (deterioration) of the blood-aqueous barrier ("BAB") and of the blood-retinal barrier ("BRB") in mammal eyes. Generally, a reduced BRB breakdown is a desirable condition or state, as it indicates a stabilized or more normal or more healthy retina (tightened barrier). On the other hand, where in a model system a BAB breakdown is induced, it is considered a positive or beneficial result if upon intravitreal administration of a steroid, such as a corticosteroid or an anti-inflammatory steroid into an eye with BAB breakdown, an improvement of the BAB breakdown is not observed. Failure of BAB breakdown to be reduced or repaired is an indication that the steroid intravitreally administered has not in significant quantity made it's way (i.e. by diffusion and/or by an active transport mechanism) to the aqueous (or anterior) chamber ("AC") of the eye. It is known that AC presence of various steroids can cause increased intraocular pressure (elevated IOP) is symptomatic of glaucoma and/or cataract generation.

SUMMARY

The experiment was carried out using intravitreal injection of either a 1 mg or 4 mg triamcinolone acetonide gel suspension (TAA<sub>aq</sub>) (the Example 8 and 9 formulations, respectively) in a rabbit model of VEGF-mediated blood-aqueous barrier (BAB) and blood-retinal barrier (BRB) breakdown. The model system used is set forth in Edelman et al., Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown, Exp Eye Res 2005 February; 80(2):249-58, although instead of intravitreal injection of a triamcinolone acetonide saline suspension, the formulation of Examples 8 and 9 above were used in this experiment.

BAB breakdown was measured by anterior chamber fluorophotometry. BRB breakdown was measured by vitreal fluorophotometry and subjective grading of fluorescein angiograms. In addition, VEGF-induced changes in vessel caliber and tortuosity (AVC-T) were assessed by subjective scoring of fundus images. The equipment and procedures used to obtain anterior chamber fluorophotometry, vitreal fluorophotometry, fluorescein angiograms, and fundus images were as set forth in Edelman (2005) supra.
The results obtained in this experiment can be summarized as follows:

1. Intravitreal 1 mg TAA<sub>sp</sub> had no effect on VEGF-induced BAB at any time point as compared to control eyes.

2. Intravitreal 1 mg TAA<sub>sp</sub> significantly inhibited VEGF-induced BRB and AVC-T through at least 6 weeks.

3. Intravitreal 4 mg TAA<sub>sp</sub> did not significantly inhibit VEGF-induced BAB breakdown at 10, 22, and 30 weeks.

Methods

Female Dutch Belt rabbits (5 to 6 months old) were randomly assigned to a no treatment group (control; n=12 eyes), to a group to receive intravitreal injection of 1 mg TAA<sub>sp</sub> (n=8 eyes), or to a group to receive intravitreal injection of 4 mg TAA<sub>sp</sub> (n=10 eyes). 50 μL of the 2% or 8% (Example 8 and Example 9 formulations respectively) TAA<sub>sp</sub> formulations were intravitreally injected into eyes of the later two groups on Day 1. Since the VEGF responses are transient and return to baseline by one week (See Edelman et al. (2005), supra), the TAA<sub>sp</sub> duration of action was determined by injecting VEGF intravitreally at multiple time points over a 10 week for 1 mg TAA<sub>sp</sub> and over a 30 week for the 4 mg TAA<sub>sp</sub>. Thus, the VEGF was injected intravitreally at 2 weeks, 6 weeks and 10 weeks after study initiation for the 1 mg TAA<sub>sp</sub> study rabbits. The VEGF was injected intravitreally at 2 weeks, 6 weeks and 10 weeks, 14 weeks, 22 weeks, and 30 weeks after study initiation for the 4 mg TAA<sub>sp</sub> study rabbits.

Drug (TAA<sub>sp</sub>) Injection

General anesthesia was initiated by isoflurane inhalation and the ocular surface was anesthetized with 1-2 drops of 1% proparacaine. Rabbits were then placed on a heated pad, covered with a sterile drape, and both eyes were treated with Betadine for 30 seconds and rinsed with sterile saline. 50 μL of the 1 mg or 4 mg TAA<sub>sp</sub> formulations (the Example 8 and 9 formulations, respectively) were administered via their original glass syringes and 27 gauge needle, and each syringe needle was calibrated to the blue line prior to injection. The syringe needle was inserted about 3 mm posterior to the limbus and aimed inferior and posterior. After injection, the needle was removed and the eye was checked for leakage.

Rabbit Model of VEGF-Induced Vasculopathologies

The Edelman (2005) A model of BRB and BAB breakdown was used to determine the pharmacologic duration of action after intravitreal injection of 1 and 4 mg TAA<sub>sp</sub>. Rabbits were placed on a heated pad, covered with a sterile drape, and 500 mg of recombinant human vascular endothelial growth factor (165 amino acid variant; VEGF<sub>165</sub>, obtained from R & D Systems, Minneapolis, Minn.) in 50 μL sterile phosphate buffered saline was injected intravitreally into all eyes via a 27G needle.

Forty-Eight hours after VEGF injection, eyes were dilated with 10% phenylephrine HCl and 1% cyclopentolate HCl. Anesthesia was induced via subcutaneous injection of 50 mg/kg ketamine and 10 mg/kg xylazine. Once anesthetized, the rabbit fundus was visualized with a Zeiss retinal camera and fundus images were obtained and stored on a personal computer. Sodium fluorescein was administered intravenously (11.75 mg/kg) and late phase angiograms were obtained after 5-10 min. Fifty minutes after fluorescein injection BRB and BAB integrity were measured using scanning ocular fluorophotometry (Fluorotron Master).

Fundus images were graded on a scale of 1 (normal) to 5 (maximal blood vessel dilation and tortuosity) by three masked observers. Retinal fluorescein leakage was scored from angiograms read by masked observers on a scale of 1 (no fluorescein leakage) to 5 (maximum fluorescein leakage).

Angiogram and fundus image scores were compared with an unpaired non-parametric Wilcoxon Rank Sum/Mann-Whitney U-Test. Fluorophotometric measurements (area under the curve) were analyzed with a two tailed Students t-test. P-values < 0.05 are determined to be significant.

Results

2% TAA<sub>sp</sub>: 1 mg dose

1. Effect on blood-retinal barrier (BRB) breakdown. Subjective grading of angiograms (FIG. 1) or vitreal fluorophotometry (FIG. 2) shows that VEGF-induced BRB breakdown was suppressed in eyes treated with 1 mg TAA<sub>sp</sub> through at least about six weeks.

2. Effect on changes in retinal vessel caliber-tortuosity (AVC-T). Subjective grading of fundus images (FIG. 3) shows that VEGF-induced AVC-T was suppressed in eyes treated with 1 mg TAA<sub>sp</sub> through at least about six weeks.

3. Effect on blood-aqueous barrier (BAB) breakdown. Anterior chamber fluorophotometry shows that the extent of VEGF-induced BAB breakdown was not suppressed in rabbit eyes treated with the 1 mg TAA<sub>sp</sub> for at least about 10 weeks (FIG. 4).

8% TAA<sub>sp</sub>: 4 mg Dose

1. Effect on BRB breakdown. Subjective grading of angiograms (FIG. 1) or vitreal fluorophotometry (FIG. 2) shows that VEGF-induced BRB breakdown was suppressed in eyes treated with 4 mg TAA<sub>sp</sub> for about between fourteen weeks (FIG. 1) and twenty weeks (FIG. 2).

2. Effect on AVC-T. Subjective grading of fundus images (FIG. 3) shows that VEGF-induced AVC-T was clearly suppressed in all eyes treated with 4 mg TAA<sub>sp</sub>, for at least fourteen weeks, and for some rabbits through twenty two to thirty weeks (210 days or about 7.5 months).

3. Effect on BAB breakdown. Anterior chamber fluorophotometry (FIG. 4) shows that the extent of VEGF-induced BAB breakdown was not significantly suppressed at 10, 22, and 30 weeks.

These results showed significant inhibition of VEGF-induced BRB responses for at least six weeks with intravitreal 1 mg TAA<sub>sp</sub> (FIGS. 1-3), and for at least 30 weeks with intravitreal 4 mg TAA<sub>sp</sub> (FIG. 3). Note that FIG. 5 is a negative image of a photograph of the eye of a rabbit in this Example 11 thirty weeks after intravitreal injection of 50
µL of the 4 mg TAA_{gs} formulation) shows that our TAA_{gs} formulation can remain intact in the vitreous for a prolonged period. In FIG. 5 item A is the intact, single object (bolus) intravitreal 4 mg, 50 µL TAA gel suspension 30 weeks after intravitreal injection. B is the vitreous chamber and C is a light reflection artifact.

Thus, based upon a demonstrated therapeutic effect for as long as thirty weeks after intravitreal injection of a TAA gel formulation, which TAA_{gs} which remains intact in the vitreous for the same period, our TAA_{gs} formulation can be characterized as a sustained release, biocompatible, biodegradable implant.

Thus, the results from this experiment demonstrate that intravitreal administration of a TAA_{gs} formulation can be used to treat a retinal disease or condition (such as a retinal disease or condition which includes BRB breakdown or deterioration) with no or little diffusion of drug to the anterior chamber (as determined for example by the Example 10 data, and by the lack of or a reduced effect on BAB breakdown set forth in this Example 11). It can therefore be concluded that our TAA_{gs} formulations can be used to advantageously treat a retinal disease or condition with, for example, little or no IOP elevation (with reduced incidence of glaucoma therefore) and with no or little inducement of cataract formation or intracranial inflammation.

Our TAA_{gs} formulations have numerous novel and advantageous characteristics making them well suited for the treatment of ocular conditions, such as posterior ocular conditions, such as macular edema, such as diabetic macula edema. For example our TAA_{gs} formulation (for example the Examples 8 and 9 formulations) do not contain any preservatives or excipients such as an alcohol (such as a benzyl alcohol) or a polysorbate (such as a polysorbate 80). Thus our TAA_{gs} formulations have a reduced toxicology.

Additionally, our TAA_{gs} formulations have superior depot and release characteristics. Intravitreal injection of an aqueous (i.e. in saline) solution of a triamcinolone provides active agent which quickly (in a matter of hours) diffuses out of the retina. Our TAA_{gs} formulations have a longer duration of intravitreal therapeutic activity because therapeutic amounts of the triamcinolone can diffuse out of the gel over a period of thirty weeks or more. Thus, use of a suspending agent such as a polymeric hyalurionate can provide the consistency permitting substantially zero order kinetics release of the triamcinolone form the hyalurionate, proving thereby both an extended duration of effect of the triamcinolone and reduced levels and therefore a reduced effect of the triamcinolone upon the anterior chamber of the eye and a reduced systemic exposure to the active agent.

Our invention comprises triamcinolone acetonide injectable gel suspensions formulated viscous suspensions of triamcinolone acetonide at concentrations of, for example, 8% and 2% with sodium hyaluronate, sodium chloride, dibasic sodium phosphate (heptahydrate), monobasic sodium phosphate (monohydrate), and water for injection. The triamcinolone acetonide injectable gel suspensions are preferably at physiologic pH, isotonic, and preservative-free. Triamcinolone acetonide injectable gel suspensions within the scope of our invention can be supplied in single-use glass syringes with fixed 27 gauge needles. The syringes can be overfilled to 0.17-0.18 mL, and calibrated to deliver 0.05 mL when primed to a black mark on the barrel of the syringe to thereby deliver, for example, 2% and 8% suspensions of 1 mg and 4 mg of triamcinolone, respectively. Our triamcinolone acetonide injectable gel suspensions can be defined as implants which upon injection (i.e. implantation) into the vitreous provided sustained release (i.e. over a period of up to seven months or longer) from the compact gel bolus injected.

Our triamcinolone acetonide injectable gel suspensions are preferably not used as visualizing agents, for example in conjunction with a vitrectomy (see eg U.S. Pat. No. 6,395,294) because the viscous, gel nature of our formulations prevents them for rapidly spreading out within the vitreous, as is required for a vitreal visualization agent (such as for example triplan vision blue, or water or saline based triamcinolone solutions or formulation, such as Kenalog®). A lower molecular weight hyalurionate with triamcinolone acetonide can be used for visualization (for example with a viscosity at a shear rate of about 0.1/second of less than about 90,000 cps, such as for example about 1,000 to 10,000 cps), whereas the higher molecular weight hyalurionate of Examples 8 and 9 are preferred for use as in situ forming vitreous implants.

Example 12

Treatment of Macular Edema with Intravitreal Triamcinolone Acetonide Suspension

A 64 year old obese female patient with symptoms of diabetes presents with vision loss due to macula edema with central retinal vein occlusion and/or branch retinal vein occlusion. She receives intravitreal injection of 4 mg of a high viscosity triamcinolone acetonide (polymeric hyaluronate based) suspension, such as the Example 9 formulation.

Twelve months after injection she demonstrates an improved best corrected visual acuity of fifteen or more letters from baseline as determined using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart.

Example 13

Treatment of a Posterior Ocular Condition with Intravitreal Triamcinolone Acetonide Suspension

Patients with a posterior ocular condition (such as a macular edema, uveitis, or macular degeneration) can be treated by intravitreal injection of 1 mg or 4 mg of a high viscosity triamcinolone acetonide gel (polymeric hyaluronate based) suspension, such as the Example 8 or Example 9 formulation. Alternately, the formulation can be administered by subconjunctival injection to treat the posterior ocular condition. These patients can demonstrate twelve months after injection an improved best corrected visual acuity of fifteen or more letters from baseline as determined using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart.

In clinical studies being carried out for the treatment of macula edema, participated in, or supervised by the inventors or their colleagues over one thousands patients have received intravitreal injection of the Example 8 or Example 9 formulations. Yet the incidence of aseptic endophthalmitis in these numerous patients has been 0%.
This is striking when one notes that the incidence of endophthalmitis upon intravitreal injection of Kenalog is about 1% to 2%.

[0175] Thus, it is important to note that the desired therapeutic result (maintained or improved vision) can be obtained with little or no incidence of intraocular inflammation. Without wishing to be bound by theory we can postulate reasons for this exceptional result. Macrophages are involved with the removal of particulate material from the body through phagocytosis. However, particles of large morphology and irregular geometry can be toxic to macrophages and lead to cell death. The death of macrophages can lead to release of pro-inflammatory cytokines that cause both acute and chronic inflammation. Clinical examples of toxicity from particles include gouty arthritis, where urate crystals that range from 5 to 20 microns cause a debilitating arthritis. Hellwell P., Use of an objective measure of articular stiffness to record changes in finger-joints after intra-articular injection of corticosteroid, Ann Rheum Dis 1997; 56:71-73. Macrophages are injured when phagocytosing the urate crystals and this initiates the inflammatory response. When patients are treated with medication that reduces macrophage activity, such as colchicine, this leads to a dramatic improvement in the arthritis. Another example of joint inflammation related to particles is ‘crystal-induced synovitis,’ where 1-2% of patients that receive intra-articular injections of Lederspan, Kenalog, or other corticosteroid depot formulation, develop a post-injection exacerbation of the joint inflammation. McCarty D., et al., Inflammatory reaction after intrasynovial injection of microcrystalline adrenocorticosteroid esters, Arthritis and Rheumatism, 7(4); 359-367 (1964). The particles in these formulations, which are on the average over 10 microns and have irregular morphology, are very similar to the urate crystals in joint of patients with gout. Significantly, in our formulations the triamcinolone particles (crystals) are not available to and/or are substantially ignored by macrophages due to the aggregation (suspension) of the triamcinolone particles in the high molecular weight hyaluronicate in our formulations. The fact that our triamcinolone formulations are in situ forming implants can also limit the exposure of whole or individual triamcinolone crystals to sensitive ocular tissues, concomitantly thereby limiting macrophage activation and hence also limiting or preventing an intraocular inflammatory response. It is important to note that with our formulation the particular high viscosity hyaluronic acid polymer chosen maintains the triamcinolone crystals in a collective matrix that acts as a sustained-release reservoir which decreases the need for frequent repeat injections. Thus, our formulation forms a cohesive agglomerate upon intra-vitreal injection. The reduced surface area of such an agglomerate facilitates provision and maintenance of a lower release rate of the triamcinolone, as compared to much larger surface area saline suspension of a triamcinolone (such as Kenalog). The cohesiveness of our formulation is exemplified by the fact that the formulation maintains its internal consistency (i.e. its shape after injection) for at least about 30 weeks after intravitreal injection (see FIG. 8).

[0176] Additionally, the compositions of our invention are preferably formulated with hyaluronic acid, a material known for its anti-inflammatory abilities. Dea I. et al., Hyaluronic acid: a novel, double helical molecule, Science, 1973 Feb. 9; 179(4056):2).

[0177] Furthermore, the absence of preservatives and/or stabilizers (such as benzyl alcohol and polysorbate 80) in our formulation reduces the retinal toxicity of our formulations as compared to formulations which contain one or more preservatives and/or stabilizers.

[0178] The combination of these five factors (lack of injury to macrophages, low availability of the triamcinolone crystal to macrophages, use of a biocompatible polymer, use of a high viscosity biocompatible polymer, and absence of preservatives and stabilizers) provides an optimal ophthalmic delivery system which limits the incidence of post-injection aseptic endophthalmitis.

[0179] A preferred embodiment of our invention can be the Example 8 and 9 formulations in which the average diameter of the triamcinolone particles present in the formulations is less than 10 microns and preferably less than 5 microns, and additionally with a uniform (spherical) morphology. It has been shown in the pulmonary literature that micronized particles of corticosteroids, <10 microns, and preferably <5 microns, are less injurious to macrophages, and have the potential for less inflammation. (Robert A. Freitas Jr., Nanomedicine, Volume II: Biocompatibility, Landes Bioscience, Georgetown, Tex., 2003). Thus, preparing our formulations with a median triamcinolone particle size of <5 microns and with uniform shape provides formulation which are even more biocompatible in the vitreous and with less propensity to cause intracocular inflammation.

Example 14

Six Month Ocular and Systemic Pharmacokinetics of Triamcinolone Acetonide Following Intravitreal Injection of 2% (1 mg) and 8% (4 mg)

Triamcinolone Acetonide Injectable Gel Suspension Formulations in Rabbit Eyes

[0180] An experiment was carried out to compare the ocular and systemic pharmacokinetics of triamcinolone acetonide (TA) following a single unilateral intravitreal injection of 2% (1 mg) and 8% (4 mg) TA injectable gel suspensions in New Zealand white rabbit eyes. These suspensions are the TA formulations of Examples 8 and 9, respectively.

[0181] Seventy-two female New Zealand White rabbits were obtained from Harlan (Indianapolis, Ind.). The rabbits were specific pathogen free (SPF), 17-18 weeks old and weighed 2.58-3.15 kg at the time of dosing. The seventy-two female rabbits were intravitreally injected with one of two TA doses (2% or 8%) and ocular and systemic pharmacokinetics monitored. Rabbits (four per group) were sacrificed on days 2, 4, 11, 32, 64, 92, 121, 151 and 183 for aqueous humor (AH), vitreous humor (VH) and plasma drug levels determined at such each time point at each of these three physiological locations. Samples were quantified using validated LC-MS/MS methods with assay range for TA of 0.2-20 ng/mL in plasma, 1-500 ng/mL in AH and 0.4-100 pg/mL in VH.

[0182] This study was a single treatment, parallel design, with 18 treatment groups and non-serial samples collected from each animal, as shown by Table 6.
The seventy-two rabbits received a single unilateral (right eye) intravitreal injection of either 2% (1 mg) or 8% (4 mg) TA gel suspension. On day 1 each rabbit received an intravitreal injection into the midvitreous region through the dorsotemporal quadrant of the right eye, approximately 2-3 mm posterior to the limbus. For each injection, the needle of a pre-filled syringe (2% and 8% TA pre-filled syringes) was introduced through the dorsotemporal quadrant of the eye, approximately 2-3 mm posterior to the limbus, with the bevel of the needle directed downward and posteriorly to avoid the lens. 50 μL of either the 2% or 8% formulation was injected in a single bolus at a location roughly in the center of the vitreous.

There were no drug-related effects on body weight and mortality. Following a single intravitreal injection of either 2 or 8% TA gel suspension, TA was detected in the is AH, VH and plasma at the earliest timepoint of Day 2. No contralateral diffusion of TA to the untreated eyes was detected in AH. The AH mean maximal concentrations (C_{max}) for 2% and 8% TA gel suspension were 27.6 ng/mL (Day 2) and 29.5 ng/mL (Day 11), respectively. The AH drug levels for the 2% and 8% dose were detectable up to Day 32 (4.15 ng/mL) and Day 151 (3.55 ng/mL), respectively. The area under the AH concentration time curve (AUC_{0-151}) was dose-dependent for the 2% (328 ng-day/mL) and 8% (1311 ng-day/mL) gel suspension with half-life (t_{1/2}) of 12.4 and 94.1 days, respectively.

Following intravitreal injection of 2% and 8% TA gel suspension, VH concentration of TA declined from 444 pg/g (57.6% dose remaining) at 2 days postdose to 22.1 μg/g (3.4% dose remaining) by 32 days post dose and 1460 μg/g (51.2% dose remaining) at 2 days to 33 μg/g (1.3% dose remaining) by 151 days post dose, respectively. No contralateral diffusion of TA to the untreated eyes was detected in VH at all timepoints except for the 8% dose on Day 2 (0.306 pg/g). The AUC_{0-151} for the 2% and 8% doses were 3410 pg-day/g and 68800 pg-day/g, respectively. The t_{1/2} for the 2% and 8% doses were 8.57 and 32.8 days, respectively. This 33 day half life is significantly greater than the 15 day half life reported for a saline suspension of TA (such as is Kenalog) in the vitreous (Aubren (2004), supra). The 33 day half life can be expected to increase significantly to a half life of about 50-60 days in the VH of pathological and/or vitrectomized eyes.

The plasma C_{max} (Day 2) for the 2% and 8% doses were 4.12 ng/mL and 3.59 ng/mL, respectively. Plasma TA was detected for the 2% and 8% dose up to Day 11 and Day 64, respectively. The AUC_{0-151} for the 2% and 8% doses were 18.1 ng-day/mL and 83.6 ng-day/mL, respectively. The t_{1/2} for the 2% and 8% doses were 3.11 and 16.2 days, respectively.

Significantly (as noted above), TA was detected in the VH for the 2% (1 mg) and 8% (4 mg) TA gel suspension for up to 1 and 5 months postdose, respectively. The systemic exposure to TA following intravitreal injection was low and is expected to be relatively safe compared to systemic exposure of oral TA. Thus, it can be concluded that at least our 8% TA gel suspension can release TA into the vitreous over at least a 5 month (151 day) period, in the manner therefore of an in situ forming sustained release implant.

Example 15

Method for Making Injectable Triamcinolone Acetonide Gel Suspension Formulations

Preferred methods were developed for making the formulations of Examples 1 to 9.

The triamcinolone formulations are made as sterile, uniform, opaque white gel suspensions suitable for intraocular (such as intravitreal) injection. The manufacturing process involves two main stages: 1) sterile suspension bulk compounding and 2) aseptic filling. The bulk product manufacture includes preparations of three separate parts, followed by aseptic combination of these three parts. The aseptic filling operation is conducted in a class 100 environment, and the sterile bulk product may be filled into pre-sterilized ready-to-use syringes.
Micronized triamcinolone acetonide, USP, was purchased from Pfizer, Inc., Kalamazoo, MI. Typical and most useful particle sizes for this drug are 4-8 microns in diameter. Sodium hyaluronate powder was purchased from Hyaluron, Woburn, Mass. Typical and most useful molecular weights for this polymer are 1.0 to 1.9 million Daltons. When used, SBE6-β-cyclodextrin (Captisol®) was obtained from CyDex, Inc., Overland Park, KS.

Part I is prepared in a main batch vessel that has capabilities of bulk heat sterilization and viscous fluid mixing. First, water for injection (WFI) at 40% of batch size is charged into the vessel and sodium chloride is dissolved. Triamcinolone powder is then added and dispersed with strong agitation. The suspension is heated and sterilized at above 120°C for a sufficient time period by steam passing through the jacket of the vessel. After the bulk heat cycle is completed, the suspension is cooled down to room temperature.

Part II is prepared in an open vessel equipped with a top entering, variable speed mixer. First, WFI at 10% of batch size is charged into the vessel. Sodium phosphate salts and, optionally, a β-cyclodextrin derivative is added and dissolved. If necessary, the pH of the solution is adjusted with 1 N sodium hydroxide and/or 1 N hydrochloric acid. When a beta cyclodextrin is used in the formulation can be dissolved along with the phosphate salts in this part II.

Part III is prepared in a Class 100 environment through a series of aseptic procedures. First, sodium hyaluronate is dissolved in WFI at dilute concentration, e.g., 0.2% w/w. The solution is sterile-filtered and sodium hyaluronate powder is recovered through bulk lyophilization. Finally, the sodium hyaluronate powder is reconstituted with sterile WFI at 50% of batch size.

Sterile bulk suspension is compounded by aseptically combining (mixing) the three parts. First, Part II solution is filtered into sterile Part I in the main batch vessel using a 0.2 micron sterilizing grade filter. Part III is then aseptically transferred into the main batch vessel. Finally, the bulk is blended (mixed) under low shear conditions to achieve uniformity. The final bulk suspension is held in a controlled area before aseptic filling.

Aseptic filling operations are performed in a Class 100 environment. Sterile bulk suspension is first filtered through a clarification screen into a sterile holding container. The bulk is then transferred to the filling machine and filled into pre-sterilized syringes. The filled units are transferred to the packaging area for application of tamper-evident seals, labeling and cartoning.

The pharmaceutical manufacturing process of this Example 15 for making triamcinolone sterile suspensions is illustrated by the FIG. 6 process flow chart.

Although not shown in FIG. 6, after Part III has been made (and before the lyophilization step is applied to Part III), Part III can be heated at about 120°C and about 130°C for between about 25-35 minutes. Doing so both sterilizes the hyaluronate and can reduce the initial 1 million to 1.9 million Daltons molecular weight of the hyaluronate used in our formulation by about 20% to about 30% (i.e. to between about 0.7 million to about 1.5 million Daltons), thereby permitting use of a higher (i.e. 30 gauge) gauge injection needle.

We carried out further experiments with the formulation of Example 9, a pharmaceutical composition comprising 8% triamcinolone acetonide in polymeric hyaluronic acid, referred to herein by the trade name Trivaris or Trivaris 8%. The findings set forth herein apply as well to the Example 8 formulation (Trivaris 2%). We confirmed the low immunogenicity or anti-inflammatory nature of Trivaris and determined that upon intraocular administration substantially all the Trivaris triamcinolone acetonide particles are embedded within the polymeric matrix of the hyaluronic acid and that Trivaris is storage stable.

Sterile endophthalmitis is an inflammatory response that can exacerbate macular edema, cause retinal detachment, and lead to vision loss. Sterile endophthalmitis can occur upon intravitreal injections of an aqueous (low viscosity) TA formulation. For example, sterile endophthalmitis has been reported with aqueous (low viscosity) TA formulations, such as Kenalog-40, that contain the preservative benzyl alcohol. Significantly, sterile endophthalmitis has also been reported with intravitreal injection of preservative-free TA formulations so the presence of the preservative in Kenalog-40 may not be the primary cause of the cases of sterile endophthalmitis it can cause.

A major factor associated with the inflammatory reaction characteristic of sterile endophthalmitis can be the drug particle burden in the vitreous cavity, as evidenced by the plume effect, which occurs upon intravitreal injection of an aqueous (low viscosity) TA formulation. Thus, individual drug particles are recognized by macrophages resident in the vitreous as they attempt to phagocytose floating drug particles. Phagocytosis leads to cytokine release and both neutrophils and macrophages are thereby recruited to the vitreous cavity. The enormous numbers of indigestible drug particles released into the vitreous by a aqueous TA formulation (with or without a preservative) can be lethal to macrophages and neutrophils, causing these cells die and release lysosomal contents, oxidative enzymes, and more proinflammatory cytokines. This results in an acceleration of the inflammatory reaction and hence the clinical manifestations of sterile endophthalmitis.

Due to their higher density triamcinolone acetonide drug particles injected into the is vitreous agglomerate into consolidated drug depots within the first week following intravitreal injection. Therefore, the risk of sterile endophthalmitis occurring is generally within the 48 hour period after intravitreal injection as this is the time when the macrophages have greatest access to the still free floating, individual drug particles.

Three lots of Kenalog-40 were examined (see FIG. 7) and it was determined that the TA particles in Kenalog can be as large as 80 microns, with high particles size variability. The heterogeneous population of drug particles in Kenalog-40 ranging in size from about 2 to about 80 microns can be injurious to phagocytes since larger and irregularly shaped drug particles are poorly ingested by such cells resulting in phagocyte cell death. This toxic inflammatory reaction to corticosteroid crystals has also been observed following
intra-articular injections where an inflammatory joint reaction occurs within 48 hours after injection is called crystal synovitis. Other more remote causes of sterile endophthalmitis include the presence of endotoxins, extraneous particles and/or excipients in the formulation and the formulation having a pH less than 5 or greater than pH 8.

[0203] The particles size distribution of four lots of Trivaris was also examined. As shown by FIGS. 8A to 8D, the median TA particles size in Trivaris was between about 4 microns and 5 microns and 90% of the TA particles in Trivaris had a diameter of 10 microns or less. FIG. 8 also shows that about 40% of the Trivaris TA particles had a diameter between about 4 microns and about 8 microns and that about 60% of the Trivaris TA particles had a diameter between about 3 microns and about 9 microns.

[0204] The TA particle size distribution data in FIGS. 7 and 8 was obtained by light scattering using a Horiba LA 300 instrument. The line graph in FIGS. 8A, B, C and D shows the cumulative TA particle size % (area under the curve) (right hand side Y axis). Trivaris is a viscous TA formulation in which the TA drug particles are embedded in and coated by the polymeric matrix of the hyaluronic acid (HA) to thereby form a viscoelastic hydrogel with a viscosity of between about 130 k and about 300 k centipoises (cps) at a shear rate of about 0.1 second at 25°C. Significantly, the TA drug particle sizes in Trivaris are deliberately uniform in distribution with a median particle size ranging from about 4 to about 6 microns. This hydrogel formulation of Trivaris can be injected through a hypodermic (syringe) needle having a needle gauge as small as 33 gauge.

[0205] The HA in Trivaris creates a physical barrier to free movement of the embedded TA drug particles, thereby reducing the potential for free floating TA particle exposure in the vitreous and resulting macrophage activation. Importantly, HA is recognized by scavenging intravitreal macrophages as a native (non-immunogenic) because there is a high concentration of HA naturally present in the vitreous humor. Thus coating the TA drug particles with HA renders the injected Trivaris formulation anti-antigenic, lowering the potential of the TA drug particles to instigate an inflammatory response. Use of HA encapsulation as an "immunologic disguise" is used in a similar fashion by some streptococcus bacterial species to evade detection and phagocytosis by macrophages and increasing the virulence of the organism. Importantly, the hydrogel formulation of Trivaris permits the TA particles to become free drug as the TA is solubilized (dissolves) in the vitreous, thereby permitting the solubilized TA to enter solution in the vitreous and then diffuse or be actively transported to the retina to treat a retinal disease or condition. The close proximity of the TA drug particles in the Trivaris HA hydrogel allows for controlled and rapid agglomeration of the TA particles as the HA gradually diffuses over time out of the depot formed upon intravitreal Trivaris injection.

[0206] An additional experiment was carried out to determine free TA particle exposure and pupillary obscuration in patients receiving either intravitreal Kenalog-40 or Trivaris. Thus a fundus photography evaluation of patients was performed one hour after each patient had received an intravitreal injection of 4 mg of either Kenalog-40 (n=4) or Trivaris (n=3). A 48 μL (50 mg) injection of the Example 98% formulation (Trivaris 8%) provided the 4 mg of TA. Note that about 100 μL of the Kenalog-40 was required to provide 4 mg of TA. The required greater (double) volume of Kenalog-40 to obtain the same amount of injected TA can by itself cause deleterious effects (such as acute elevation of intraocular pressure leading to central retinal artery occlusion) due to the limited normal vitreal volume. As shown by Table 7 it was determined that about 83% of the TA particles were floating free in the vitreous after the Kenalog injections, whereas only about 6% of the TA particles were free floating in the patients injected with Trivaris. Significantly, therefore about 84% of the Trivaris TA particles were upon intravitreal injection embedded within the HA. Additionally, the pupil was obscured with drug particles in a mean of 29.8% of the patients who received Kenalog, versus only a 1.7% pupil obscuration by TA particles in the patients who had received Trivaris.

[0207] Hence, Trivaris has minimal free TA drug particle exposure and pupil obscuration, compared with Kenalog, following intravitreal injection.

[0208] The low numbers of drug particles in an unbound state following injection of Trivaris can be expected to reduce activation of scavenging macrophages compared with other TA suspensions, such as Kenalog-40, where the majority of the TA particles are upon intravitreal injection exposed to macrophages and inflammatory consequences can then ensue. The effectiveness of the Trivaris formulation to reduce the median particle potential has been observed in recent clinical trials. In over 1000 patients in phase 3 clinical trials that have received injections of Trivaris formulation, some multiple times, there have been no reported cases of sterile endophthalmitis. The consolidation of the drug particles in the Trivaris HA hydrogel, with a clear view through the pupillary axis, also enables immediate recovery of vision after injection & enables PDT, thermal laser and diagnostic procedures to be performed.

[0209] A further experiment was carried out to examine the stability of the TA particles in Trivaris. We determined that the TA drug particles in the HA hydrogel suspension of is Trivaris were remarkably stable, with minimal crystal agglomeration or degradation during extended storage. Thus, 0.5 mL glass syringes were filled with 0.2 mL of the Example 9 formulation. The filled syringes were stored horizontally at 25°C, in 60% relative humidity. Upon syringe filling (time zero), at 5 weeks, at 6 weeks and after three months of storage, TA particle size was determined using laser light scattering with Horiba LA 300 instrument, after dilution of a Trivaris sample in distilled water just prior to the light scattering analysis. 90th percentile of volume-weighted size distribution data from three different lots showed that at time zero 90% of the TA particles had a diameter of 11 microns or less, at +5 weeks and at +6 weeks 90% of the TA particles still had a diameter of about 11 microns or less. Finally at +3 months 90% of the TA particles still had a diameter of about 13 microns or less. These results mean that even with prolonged storage the TA particles remain suspended in the HA and undergo neither substantial agglomeration or degradation. Hence, even after prolonged storage Trivaris retains its syringability without needle occlusion.

[0210] In addition to limiting particle exposure, the HA of Trivaris has additional inherent anti-inflammatory proper-
ties. Hyaluronic acid inhibits movement of macrophages, down regulates the production of proinflammatory cytokines and chemokines in models and human diseases, scavenges oxygen free radicals, and inhibits matrix metalloproteinases. Trivaris can include additional features to minimize an inflammatory reaction upon intravitreal injection, such as preparing Trivaris to have a pH between 6 and 7 range, and strict endotoxin and extraneous particle control.

Furthermore, the uniform population of micronized TA particles in Trivaris (see FIG. 7) provides a predictable ocular TA release pharmacokinetics with increased TA vitreous half-life.

The Example 8 and 9 Trivaris formulations can also be used as an injectable pharmaceutical composition to treat various articular (joints and spine) pathologies while at the same time reducing the potential for occurrence of post-injection inflammation (crystal synovitis).

In summary, the Trivaris formulation creates a physical barrier to free movement of drug particles to reduce the potential for particle exposure, macrophage activation, and the potential for sterile endophthalmitis. The consolidation of the TA drug particles in the HA hydrogel enables immediate recovery of vision after injection & enables PDT, thermal laser and diagnostic procedures to be performed. Incorporating a uniform population of micronized TA particles in the formulation facilitates management by macrophages when outside of the drug depot, but also leads to predictable ocular pharmacokinetics with an increased vitreous half-life. Trivaris is supplied in pre-loaded syringes with little or no endotoxin and extraneous particle content, to thereby further limit post-injection inflammation. Trivaris does not contain benzyl alcohol or any other preservatives thereby reducing toxicity to retinal cells.

Additionally, although preferably the polymeric hyaluronate in Trivaris is a non-cross linked hyaluronate (so as to obtain, upon application of force to the plunger of the syringe used to administer Trivaris, a high shear rate and hence relative ease of injection of Trivaris through a 27-33 gauge needle), the hyaluronate can alternately be a cross-linked hyaluronate (to form a true hydrogel therefore) with a significantly lower viscosity (i.e. with a viscosity of about 5,000 cps at a shear rate of about 0.1/second at about 25°C.). Such a cross-linked hyaluronate can have the same or similar excellent corticosteroid suspension property of Trivaris, and have the additional advantage of longer residency (i.e. biodegradable at a slower rate) of the hyaluronate in the vitreous, with resulting prolonged nominal immunogenicity of such a cross-linked hyaluronate formulation in the vitreous, due to a longer period of intravitreal (or intraocular) retention of the corticosteroid particles in the polymeric matrix of the cross-linked hyaluronate.

Furthermore, besides hyaluronate other cross-linked polymers can be used, such as for example a polycarbophil.

All references, articles, publications, patents and applications set forth above are incorporated herein by reference in their entireties.

We claim:

1. A pharmaceutical composition for treating a posterior ocular condition, the pharmaceutical composition comprising:
   (a) a plurality of corticosteroid particles mixed with;
   (b) a viscous polymer, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/

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**TABLE 7**

Photographic evaluation in patients following an intravitreal injection of Kenalog-40 or Trivaris 8%

<table>
<thead>
<tr>
<th>Subject</th>
<th>Kenalog-40</th>
<th>Free particles exposed %</th>
<th>Consolidated depot %</th>
<th>Posterior PoleView obscuration*</th>
<th>Pupil Obscuration**</th>
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**TOTALS**

Kenalog Mean (SD) 82.5 (8.7) 17.5 (1.29) 1.3 (0.6)

Trivaris Mean 5 60 94.0 0 1.7 (3.6) (3.6) (2.9)

*graded as Vitreous Haze (SUN Criteria) 0 through 4++
**grade as % of pupillary area (dilated) obscured by drug as measured with the red reflex photo

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto. For example, the corticosteroid formulations set forth herein can be used to treat conditions including articular pathologies, such as rheumatoid and osteoarthritis, and spinal conditions, such as facet arthritis, and the treatment of chronic pain by epidural or spinal root injections of a formulation such as a Trivaris formulation second at about 25°C., and the pharmaceutical composition can be injected into the vitreous of a human eye through a 25 to 33 gauge needle.

2. The pharmaceutical composition of claim 1, wherein the corticosteroid particles have a substantially uniform diameter.

3. The pharmaceutical composition of claim 1, wherein substantially all the corticosteroid particles are embedded within the viscous polymer.
4. The pharmaceutical composition of claim 1, wherein the corticosteroid is a triamcinolone.

5. The pharmaceutical composition of claim 1, wherein the viscous polymer is a polymeric hyaluronate or a polymeric hyaluronic acid.

6. A pharmaceutical composition for treating a posterior ocular condition, the composition comprising:
   (a) a plurality of triamcinolone particles with a substantially uniform diameter, and;
   (b) a viscous polymeric hyaluronate or polymeric hyaluronic acid, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25°C, and can be injected into the vitreous of a human eye through a 25 to 33 gauge needle, wherein the triamcinolone particles are mixed with the viscous polymer substantially all the corticosteroid particles are embedded within and coated by the viscous polymeric hyaluronate or a polymeric hyaluronic acid.

7. A method for treating a posterior ocular condition, the method comprising the step of injecting into the vitreous of a patient’s eye with a posterior ocular condition a viscous pharmaceutical composition comprising a plurality of corticosteroid particles mixed into a viscous polymeric matrix, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25°C, such that about one hour after the intravitreal injection only about 10% or less of the corticosteroid particles are present in the vitreous free of the polymeric matrix.

8. The method of claim 7, wherein about one hour after the intravitreal injection only about 5% or less of the corticosteroid particles are present in the vitreous free of the polymeric matrix.

9. The method of claim 7, wherein about one hour after the intravitreal injection only about 3% or less of the corticosteroid particles are present in the vitreous free of the polymeric matrix.

10. A process for making an intraocular pharmaceutical composition, the method comprising the step of mixing an aqueous suspension of a plurality of corticosteroid particles and an aqueous solution of a viscous polymeric matrix, so that the resulting pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25°C.

11. The process of claim 10, wherein the corticosteroid particles have a median particle size of between about 4 microns and about 5 microns.

12. The process of claim 10, wherein the corticosteroid particles have a stable diameter for at least three months after the pharmaceutical has been made and stored for three months in a syringe placed horizontally at about 25°C at about 60% relative humidity.

13. The pharmaceutical composition made by the method of claim 10.

14. A pharmaceutical composition for treating an articular pathology, the pharmaceutical composition comprising:
   (a) a plurality of corticosteroid particles mixed with;
   (b) a viscous polymer, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25°C.

15. A method for treating an articular pathology, the method comprising the step of injecting into a joint of a patient with an articular pathology a viscous pharmaceutical composition comprising a plurality of corticosteroid particles mixed into a viscous polymeric matrix, wherein the pharmaceutical composition has a viscosity of between about 130,000 cps and about 300,000 cps at a shear rate of about 0.1/second at about 25°C.

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