1. **NAME OF THE MEDICINAL PRODUCT**
   Prednisolone Acetate Ophthalmic Suspension USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

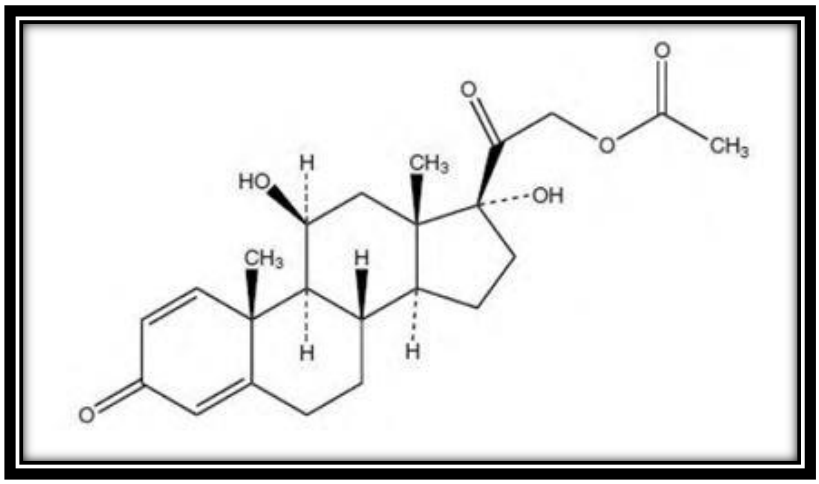
Qualitative Declaration:
Prednisolone Acetate Ophthalmic Suspension USP

Chemical Name:
[2-[(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-Dihydroxy-10,13-dimethyl-3-oxo-7,8,9,11,12,14,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl]-2-oxoethyl] acetate

Molecular Weight: - 402.49 g/mol

Molecular Formula: - $C_{23}H_{30}O_6$

Structural Formula:-



Pharmaceutical Form Visual description of the appearance of product:
Milky white to off-white suspension.

Quantitative Declaration:
Composition: w/v

Prednisolone Acetate	USP	1.0% w/v
Benzalkonium Chloride Solution (As Preservative)	NF	0.01% w/v
Sterile Aqueous Base		Q.s

3. PHARMACEUTICAL FORM

Eye Drops

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

INDICATIONS AND USAGE

Prednisolone Acetate Ophthalmic Suspension USP is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

4.2 Posology and method of administration

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated (see PRECAUTIONS).

4.3 Contraindications

Contraindications

Contraindicated in patients with acute, untreated, purulent ocular infections; acute superficial herpes simplex (dendritic keratitis); vaccinia, varicella, or other viral or fungal eye diseases; or ocular tuberculosis. Use cautiously in patients with corneal abrasions that may be contaminated (especially with herpes).

4.4 Special warnings and precautions for use

WARNINGS

Prolonged use of corticosteroids may result in posterior subcapsular cataract formation and may increase intraocular pressure in susceptible individuals, resulting in glaucoma with damage to theoptic nerve, defects in visual acuity and fields of vision. Prolonged use may also suppress the host immune response and thus increase the hazard of secondary ocular infections.

If this product is used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be checked frequently. Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation.

Acute purulent infections of the eye may be masked or activity enhanced by the presence ofcorticosteroid medication.

The use of steroids after cataract surgery may delay healing and increase the incidence of blebformation.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution; frequent slit lamp microscopy is recommended.

Prednisolone Acetate Ophthalmic Suspension USP suspension contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

General

The initial prescription and renewal of the medication order beyond 20 milliliters of Prednisolone Acetate Ophthalmic Suspension USP suspension should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

As fungal infections of the cornea are particularly prone to develop coincidentally with longterm local corticosteroid applications, fungal invasion should be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted in animals or in humans to evaluate the potential of these effects.

Pregnancy

Prednisolone has been shown to be teratogenic in mice when given in doses 1-10 times the human dose. Dexamethasone, hydrocortisone, and prednisolone were ocularly applied to both eyes of pregnant mice five times per day on days 10 through 13 of gestation. A significant increase in the incidence of cleft palate was observed in the fetuses of the treated mice. There are no adequate well-controlled studies in pregnant women. Prednisolone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenouscorticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from prednisolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness in pediatric patients have been established. Use in pediatric patients is supported by evidence from adequate and well-controlled studies of prednisolone acetate ophthalmic suspension in adults with additional data in pediatric patients.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

4.5 Interaction with other medicinal products and other forms of interaction

ADVERSE REACTIONS:

Adverse reactions include, in decreasing order of frequency, elevation of intraocular pressure (IOP) with possible development of glaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing. Although systemic effects are extremely uncommon, there have been rare occurrences of systemic hypercorticoidism after use of topical steroids. Corticosteroid-containing preparations have also been reported to cause acute anterior uveitis and perforation of the globe. Keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation and ptosis have occasionally been reported following local use of corticosteroids. The development of secondary ocular infection (bacterial, fungal and viral) has occurred. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used (SEE WARNINGS).

4.6 Fertility, pregnancy and lactation

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
before using prednisolone, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients (such as sulfites found in some brands), which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: eye infections, recent eye surgery, cataracts, glaucoma (open-angle type), severe nearsightedness (myopia), diabetes.

After you apply this drug, your vision may become temporarily unstable. Do not drive, use machinery, or do any activity that requires clear vision until you are sure you can perform such activities safely.
Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).

If you develop a new eye infection or injury, or require eye surgery, ask your doctor if you should continue to use your current bottle of prednisolone eye drops or start a new bottle.

During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor.

It is not known if the medication in this product passes into breast milk. Consult your doctor before breast-feeding.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenouscorticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from prednisolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

4.7 Effects on ability to drive and use machines

Prednisolone Acetate Ophthalmic Suspension USP may cause short-lasting blurring of vision upon instillation. If affected, the patient should not use machinery/electric tools or drive until vision has returned to normal.

4.8 Undesirable effects

SIDE EFFECTS

The following adverse reactions have been identified during use of PRED FORTE®. Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions include elevation of intraocular pressure (IOP) with possible development ofglaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing.

The development of secondary ocular infection (bacterial, fungal, and viral) has occurred. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used (see PRECAUTIONS).

Other adverse reactions reported with the use of prednisolone acetate ophthalmic suspension include: allergic reactions; dysgeusia; foreign body sensation; headache; pruritus; rash; transient burning and stinging upon instillation and other minor symptoms of ocular irritation; urticaria; and visual disturbance (blurry vision).

Keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodationand ptosis have occasionally been reported following local use of corticosteroids. Corticosteroid-containing preparations have also been reported to cause acute anterior uveitis and perforation of the globe.

4.9 Overdose

This medicine may be harmful if swallowed. If someone has overdosed and has serious symptoms such as passing out or trouble breathing, call 911. Otherwise, call a poison control center right away. US residents can call their local poison control center at 1-800-222-1222. Canada residents can call a provincial poison control center.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacodynamic properties:

Prednisolone is a synthetic glucocorticoid used as antiinflammatory or immunosuppressive agent. Prednisolone is indicated in the treatment of various conditions, including congenital adrenal hyperplasia, psoriatic arthritis, systemic lupus erythematosus, bullous dermatitis herpetiformis, seasonal or perennial allergic rhinitis, allergic corneal marginal ulcers, symptomatic sarcoidosis, idiopathic thrombocytopenic purpura in adults, leukemias and lymphomas in adults, and ulcerative colitis. Glucocorticoids are adrenocortical steroids and cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

Mechanism of action:

Glucocorticoids such as Prednisolone can inhibit leukocyte infiltration at the site of inflammation, interfere with mediators of inflammatory response, and suppress humoral immune responses. The antiinflammatory actions of glucocorticoids are thought to involve phospholipase A2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes. Prednisolone reduces inflammatory reaction by limiting the capillary dilatation and permeability of the vascular structures. These compounds restrict the accumulation of polymorphonuclear leukocytes and macrophages and reduce the release of vasoactive kinins. Recent research suggests that corticosteroids may inhibit the release of arachidonic acid from phospholipids, thereby reducing the formation of prostaglandins. Prednisolone is a glucocorticoid receptor agonist. On binding, the corticoreceptor-ligand complex translocates itself into the cell nucleus, where it binds to many glucocorticoid response elements (GRE) in the promoter region of the target genes. The DNA bound receptor then interacts with basic transcription factors, causing an increase or decrease in expression of specific target genes, including suppression of IL2 (interleukin 2) expression.

Description:

Prednisolone Acetate is the acetate salt form of prednisolone, a synthetic glucocorticoid with anti-inflammatory and immunomodulating properties. As a glucocorticoid receptor agonist, prednisolone acetate binds to specific intracellular glucocorticoid receptors, and

causes the ligand-receptor complex to be translocated to the nucleus where it initiates the transcription of glucocorticoid-responsive genes such as various cytokines and lipocortins. Lipocortins inhibit phospholipase A2, thereby blocking the release of arachidonic acid from membrane phospholipids and preventing the synthesis of prostaglandins and leukotrienes, both potent mediators of inflammation. This agent also decreases the number of circulating lymphocytes, induces cell differentiation, and stimulates apoptosis in sensitive tumor cell populations.

Unless otherwise directed by your doctor, do not wear contact lenses while you are using this medicine. Sterilize contact lenses according to the manufacturer's directions, and check with your doctor before you begin using them again.If your doctor does approve the wearing of contact lenses during treatment with this medication, remove the lenses before using the eye drops. The preservative in this product may be absorbed by contact lenses. Wait at least 15 minutes after each dose of the eye drop before wearing the lenses again.To apply eye drops, wash your hands first. If you are using a suspension form of this medication, shake the bottle well before using. To avoid contamination, do not touch the dropper tip or let it touch your eye or any other surface.Tilt your head back, look upward, and pull down the lower eyelid to make a pouch. Hold the dropper directly over your eye and place 1 drop into the pouch. Look downward and gently close your eyes for 1 to 2 minutes. Place one finger at the corner of your eye (near the nose) and apply gentle pressure. This will prevent the medication from draining out. Try not to blink and do not rub your eye. Repeat these steps for your other eye if so directed and if your dose is for more than 1 drop.Apply as often as directed by your doctor. Do not rinse the dropper. Replace the dropper cap after each use.If you are using another kind of eye medication (for example, other drops or ointments), wait at least 5 to 10 minutes before applying other medications. Use eye drops before eye ointments to allow the drops to enter the eye.Use this medication regularly in order to get the most benefit from it. To help you remember, use it at the same time(s) each day.The dosage and length of treatment are based on your medical condition and response to treatment. Do not use this medication more often or for longer than prescribed because doing so may increase your risk of side effects.Continue to use this medication for the full time prescribed. Do not stop using this medication without consulting your doctor. Some conditions may become worse when the drug is suddenly stopped. Your dose may need to be gradually decreased.Do not use this product if it becomes contaminated (for example, drops turn a dark color). Use of contaminated eye medication can cause infection, serious damage to the eye, and loss of

vision. Contact your doctor or pharmacist for more information.Tell your doctor if your condition does not improve after 2 days or if it worsens.

Before using prednisolone, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients (such as sulfites found in some brands), which can cause allergic reactions or other problems. Talk to your pharmacist for more details.Before using this medication, tell your doctor or pharmacist your medical history, especially of: eye infections, recent eye surgery, cataracts, glaucoma (open-angle type), severe nearsightedness (myopia), diabetes.After you apply this drug, your vision may become temporarily unstable. Do not drive, use machinery, or do any activity that requires clear vision until you are sure you can perform such activities safely.Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).If you develop a new eye infection or injury, or require eye surgery, ask your doctor if you should continue to use your current bottle of prednisolone eye drops or start a new bottle.During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor.It is not known if the medication in this product passes into breast milk. Consult your doctor before breast-feeding.

Drug interactions

The effects of some drugs can change if you take other drugs or herbal products at the same time. This can increase your risk for serious side effects or may cause your medications not to work correctly. These drug interactions are possible, but do not always occur. Your doctor or pharmacist can often prevent or manage interactions by changing how you use your medications or by close monitoring.To help your doctor and pharmacist give you the best care, be sure to tell your doctor and pharmacist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products) before starting treatment with this product. While using this product, do not start, stop, or change the dosage of any other medicines you are using without your doctor's approval.Keep a list of all the products you use. Share the list with your doctor and pharmacist to reduce your risk for serious medication problems.

5.2 Pharmacokinetics Properties

Pharmacokinetics
Absorption: After ophthalmic use, absorbed through aqueous humor. Systemic absorption rarely occurs.
Distribution: After ophthalmic use, distributed throughout local tissue layers. Any drug absorbed into circulation is rapidly removed from blood and distributed into muscle, liver, skin, intestines, and kidneys.
Metabolism: After ophthalmic use, corticosteroids primarily metabolized locally. Small amount absorbed into systemic circulation is metabolized primarily in liver to inactive compounds.
Excretion: Inactive metabolites excreted by kidneys, primarily as glucuronides and sulfates, but also as unconjugated products. Small amounts of metabolites excreted in feces.

Prednisolone acetate has been shown to penetrate rapidly the cornea after topical application of a suspension preparation. Aqueous humour T_{max} occurs between 30 and 45 minutes after installation. The half-life of prednisolone acetate in human aqueous humour is approximately 30 minutes.

Pharmacokinetics of ophthalmic corticosteroids

Corticosteroids have been used by ophthalmologists with increasing frequency over the past 30 years, with the concomitant development of a diverse range of drop, ointment, subconjunctival, and oral preparations. Though the clinical benefits and side effects of such corticosteroid preparations have been well documented, their basic pharmacokinetics in the human eye have yet to be fully established. Indeed most of our pharmacokinetic knowledge of these drugs has been elucidated by extrapolation of data obtained from rabbit experiments.1-26 These results can be significantly disparate from human data because of the thinner rabbit cornea, lower rabbit blink rate, effect of general anaesthetic, upright or recumbent position, vascularity of the rabbit orbital plexus, and small rabbit body mass. Thus, in general, measurements of steroid concentration in rabbit tend to be significantly higher than those recorded in humans.3135

Topical ophthalmic drops/ointments

These are still the most common methods of administering steroids to the eye and following a single topical drop, steroid is measurable in human aqueous humour within 15-30 minutes.3132 Not surprisingly, increased steroid concentration in topical preparations generally results in higher intraocular concentrations,'3 14 but for prednisolone acetate the optimum dose response effect in experimental keratitis occurs at a 1% concentration, and is not improved by further increases in concentration.20 Increasing ocular contact time by preparing topical steroids in a microsuspension,25 gel, or viscous formulation3536 can double the corneal and aqueous humour concentrations of steroid compared with the same drug applied as a solution.'33536 Other apparently minor changes in formulation, such as the addition of benzalkonium, can significantly alter the pharmacokinetics of topical steroids.'3 For these reasons many workers chose to use commercially prepared 'off the shelf' steroids in an attempt to unravel differences in pharmacokinetic behaviour, which may be associated with clinical efficacy.'721261321 II37 In contradistinction, the preparation of different topical steroid derivatives in an identical base vehicle has demonstrated that the greatest

barrier to intraocular penetration is the lipid rich corneal epithelium, which retards the ingress of polar, hydrophilic derivatives such as prednisolone phosphate,9 126 but is much less of a barrier to lipophilic derivatives such as the alcohol and acetate forms of dexamethasone and prednisolone.'5 16202638 Interestingly, if this epithelial barrier is removed prednisolone phosphate penetrates the cornea in much higher quantities than the lipophilic, acetate derivative.'2 These additive effects of increased concentration, lipophilic derivation, and the increased contact time afforded by a microsuspension have been demonstrated in humans, where a single drop of prednisolone acetate 1-0% microsuspension has been shown to produce intraocular steroid concentrations which were 20-fold those of a single drop of prednisolone phosphate 0 5% solution,3133 and almost 100-fold those of a single drop of betamethasone phosphate 0*l% solution.32 In contrast, when dexamethasone, prednisolone, and fluorometholone are all formulated at a concentration of 0-1% in an identical vehicle, the aqueous humour concentrations of these steroids are almost identical.'9 None the less it is essential when considering such empirical data, to recall that the systemic anti-inflammatory effect of both betamethasone and dexamethasone is five to seven times that of prednisolone.39"' The local anti-inflammatory potency of ocular steroids has yet to be fully investigated and whilst early work suggested that prednisolone acetate 1% had the greatest antiinflammatory effect in experimental keratitis,'7 later studies demonstrated that fluorometholone acetate in a 1% formulation was equally efficacious in the same model.26 However, prednisolone acetate 1 -0% drops have been shown to significantly inhibit the tear film polymorphonuclear leucocyte response to partial denudation of the corneal epithelium, whereas 0 1% concentrations of prednisolone acetate, dexamethasone, and fluorometholone are ineffective.3 As already noted, the absence of corneal epithelium can significantly affect the penetration of topical steroids, and it may also be relevant to the clinical situation that higher corneal concentrations of steroid may occur in the presence of intraocular inflammation,9 whereas the concomitant application of an antibiotic drop within 60 seconds of steroid application can reduce the bioavailability of the applied steroid by almost 70%.23 It has not been established which concentration of steroid is desirable for minor ocular inflammatory conditions such as postoperative uveitis, and whilst concentrations of 670 ng/ml of prednisolone have been recorded in human aqueous humour,33 perhaps a peak of 25 ng/ml3' might be sufficient to suppress inflammation and minimise side effects.4' For comparison, peak timolol concentrations of 2500 ng/ml have been recorded in rabbit aqueous humour following topical application, yet [receptor blockade can be obtained by as little as 9 ng/ml.42

Preparation of prednisolone acetate as a gel provides a more prolonged release43 and higher peak aqueous concentration when compared with an equivalent topical solution.24 However, some viscous agents and ointments may actually produce lower peak ocular concentrations of steroid when compared with drops.'243 Despite this, owing to prolonged release, a single application of a steroid ointment such as dexamethasone phosphate results in only 25% less overall absorption of steroid than a single drop of the same steroid. 2

It is generally believed that most of the topical and, indeed, subconjunctival steroid (see below), enters the eye via the cornea, thus radiolabelled hydrocortisone produces only 2 5% of the anticipated aqueous humour concentration when corneal penetration is prevented, compared with topical application with free access to the cornea.44 However, for other drugs such as pilocarpine and timolol, penetration into the iris and ciliary body via the non-corneal

route may account for drug concentrations which reach almost 10% of the combined corneal and non-corneal route," and such trans-scleral penetration may be even more important for larger molecules, such as inulin.4

Periocular injections

Repeated subconjunctival injections of prednisolone (50 mg) have been shown to be inferior to hourly topical prednisolone acetate 1% drops (6-5 mg) in reducing the inflammatory 681 on 11 February 2019 by guest. Protected by copyright. http://bjo.bmj.com/ Br J Ophthalmol: first published as 10.1136/bjo.76.11.681 on 1 November 1992. Downloaded from McGhee response in experimental keratitis.2' Early analytical techniques suggested that such subconjunctivally injected steroid entered the eye via the sclera.5 Indeed, the sclera is readily permeable to even relatively large molecules such as albumin,* and therefore, not surprisingly, high levels of corticosteroid can be detected in the sclera underlying a subconjunctival injection site.5 However, the greater concentration of such steroid appears to enter the eye by diffusing through the puncture site in the conjunctiva into the tear film, and thence via the cornea into the intraocular milieu.'

In this context it is not unexpected that sub-Tenon's injections of methyl prednisolone in monkeys produced significant anterior segment steroid concentrations (approx 25 ng/ml) but could only produce peak vitreous concentrations of 2 ng/ml.47 In contrast, retrobulbar methyl prednisolone in the same model produced much higher posterior uveal/retinal concentrations and significant vitreous levels which persisted for up to 9 days.48 These discrepancies might be partly explained by the lack of postequatorial diffusion of drug following subconjunctival and sub-Tenon's injections.29 It is notable that, in contrast to the enhanced corneal penetration of topical steroid drops previously noted in intraocular inflammation, when a peribulbar injection is used, total ocular steroid levels may actually be lower in eyes with intraocular inflammation compared with uninflamed eyes.2

The inherent risks of peribulbar injection of steroid (see below) and the availability ofalternative, superior methods of application, suggest to the author, in the context of the preceding data, that the role of peribulbar injection is limited to the operating room and to a few other selected situations where frequent topical medication is not practicable. The short term local use of orbital floor steroids in nonnecrotising scleritis may be such an exception to this," whereas the role of retrobulbar steroid in the treatment of persistent macular oedema remains unresolved.5

Systemic administration

When one considers the bodywide distribution of a systemically administered steroid, it is easy to comprehend the dramatically larger steroid doses required to equal the previously noted aqueous humour concentrations produced by topical drops; however, the extent of this disparity is seldom fully appreciated. In the rabbit it has been shown that an intravenous dose of 25 mg dexamethasone (equivalent to 500 mg in a 70 kg man!) was required to produce aqueous humour levels which were comparable with those achieved following topical dexamethasone alcohol drops, whereas a similar intravenous dose of prednisolone. only achieved 50% of the peak aqueous concentration obtained by four drops of methyl prednisolone 0.5%.2 Similarly, intramuscular methyl prednisolone in squirrel monkeys

produced total ocular tissue concentrations, and vitreous concentrations in particular, which were less than 1% of those obtained by a similar dose given as a periocular injection.' Indeed, maximal intraocular steroid concentration may actually represent as little as 0 5% of an intravenous dose.9 That systemic steroids have an important role in ophthalmic practice, such as the treatment of corneal graft rejection,5' is not in question, but they must be used in the knowledge that they act by primarily affecting the systemic limb of ocular disease and that there are superior, local, alternative methods of producing significant intraocular concentrations of steroid, if that is what is desired.

Coliagen shields and contact lenses

Waltman and Kaufmann demonstrated that hydrophilic con- tact lenses could be presoaked in a drug solution and used as a form of delayed release vehicle.52 A few years later Hull et al established that hydrophilic contact lenses, presoaked in 1% prednisolone phosphate, produced an aqueous humour peak concentration that was three to fourfold that obtained by application of topical drops and this advantage was maintained at 4 hours.53 The search for a topically applied, slow release drug system in other areas led to the successful development of pilocarpine ocuserts, which though not widely used, and despite some limitations, have been shown to be a viable alternative to topical drops in certain patients.54

Similarly, early soluble collagen inserts presoaked in gentamicin produced higher tear film and corneal concentrations of gentamicin than gentamicin administered in drop, ointment, or subconjunctival form.55 The development of dissolving collagen shields has rekindled interest in this method of delivering ophthalmic drugs and such shields presoaked in tobramycin have been well tolerated by patients56 and have been shown to produce higher aqueous and corneal concentrations of tobramycin than subconjunctival injections.57 Collagen shields have also been suggested as the optimum vehicle for poorly soluble drugs such as cyclosporin.58 Recently it has been demonstrated that collagen shields presoaked in dexamethasone alcohol produce superior intraocular concentrations of dexamethasone than hourly drops over the first 4 hours, and that a combination of a presoaked shield and hourly topical drops doubles the cumulative delivery of steroid to the eye at 6 hours when compared with hourly drops alone.59 For those looking for the ideal short term sustained release vehicle, and a safe yet superior alternative to subconjunctival injections, collagen shields would appear to provide increased compliance, better 24 hour control, higher ocular drug concentrations than comparable methods of administration, and good patient tolerance. However, like pilocarpine ocuserts they have yet to gain wide acceptance by clinicians and whether, like ocuserts, they will fail to gain a regular place in our pharmacological armamentarium, owing to limitations yet to be identified, remains to be seen. In a note of caution, it has already been highlighted that certain antibiotic and steroid combinations in collagen shields may provoke adverse corneal reactions.

Intravitreal injection, liposomes, and iontophoresis

Whilst intravitreal injections of antibiotics have become a standard technique in the treatment of endophthalmitis the use of intravitreal steroids in ophthalmology is less well established. Ocular dialysis has demonstrated that after subconjunctival gentamicin, virtually no gentamicin is recorded in the vitreous, whereas intravitreal injection of gentamicin may produce significant levels with a half life of up to 22 hours.6' In contrast, intravitreally injected dexamethasone appears to have a half life of 3 hours with only 10% of the peak

concentration remaining at 8 hours, although concentrations of 50 ng/ml may persist for up to 4 days.6

The incorporation of drugs into liposomes has demonstrated an up to 10 times improvement in the intraocular penetration of hydrophilic drugs following topical application.63 However, possibly because the commonly used ophthalmic steroids such as dexamethasone alcohol, prednisolone acetate, and fluorometholone are already lipophilic, there has, as yet, been little utilisation of liposome delivery for steroids. Transcorneal and trans-scleral iontophoresis of polar drugs, which normally penetrate these structures poorly, remain largely experimental, though the trans-scleral iontophoresis of dexamethasone phosphate can produce higher vitreous concentrations than the retrobulbar, subconjunctival, or topical routes.'9

Side effects of ophthalmic steroids

The adverse effects of systemic steroids are well known to ophthalmologists, therefore local administration is often seen as a logical method of minimising such side effects.49 Some local applications are not without obvious inherent risks such as bulbar perforation, choroidal injection, central retinal artery occlusion, muscle imbalance and persistently raised intraocular pressure following the periocular injection of steroids.65"7 Additionally, systemic absorption of periocular steroids in rabbits has been noted to decrease circulating lymphocytes and antibodies,27 and to reduce the total white blood cell count.22 Surprisingly, considering the small volume of steroid administered, topical drop application of steroid in rabbits produces significant liver, urine, and plasma concentrations36 and by 30 minutes almost a third of the applied steroid is distributed systemically,3 with less than 5% of the administered steroid being recoverable from the eye.39 Owing to this significant systemic dissemination of steroid, topical application inhibits corneal wound healing in both the treated and the untreated, contralateral eye in rabbits.28 In larger experimental animals, following eight drops of prednisolone acetate 1 -0% per day (4 mg of prednisolone per day), both small dogs68 and large dogs (27-41 kg)69 have exhibited adrenal suppression, though the adrenal axis is more readily suppressed in dogs than in humans.6869 In humans, the systemic absorption of topically applied drugs such as I blockers is well established,70 whereas the systemic effects of topical ocular steroids is less clearly defined, and whilst Burch71 observed a 50% decrease in endogenous steroid production in male volunteers given hourly dexamethasone 0-01% drops (0 75 mg dexamethasone per day) for 6 days. Krupin72 demonstrated a reduction in endogenous plasma cortisol but no adrenal axis suppression following eight drops of dexamethasone 0-1% per day for 6 weeks. It seems reasonable, therefore, to suggest that the possibility of adrenal suppression should be considered when ophthalmologists employ intensive topical steroids such as prednisolone acetate 1 0% and dexamethasone 0 1%.

Conclusion

Although more information on ophthalmic steroids in humans is becoming available, we still rely heavily on data derived from animal models. Fortunately, while some of the animal data are conflicting, the general trends appear to be similar in humans, though the magnitude of intraocular steroid penetration in humans appears less. The marked differences in pharmacokinetic behaviour illustrated by identical concentrations of the same steroid, in different topical drop formulations, does mean that generic equivalence cannot be assumed between preparations merely on the basis of equivalent steroid content. Topical and local

application of steroids appears preferable to systemic administration wherever possible; however, the limitations of, and alternatives to, subconjunctival injection should be carefully considered, as should the possibility of adrenal suppression following intensive ophthalmic corticosteroid drops in children and small adults.

5.3 Preclinical safety data

Clinical Studies

Abstract

Purpose. Endogenous anterior uveitis (AU), when untreated, may lead to vision loss. This study compared the safety and efficacy of difluprednate versus prednisolone acetate for the treatment of this condition.

Methods.: This phase III, double-masked, noninferiority study randomized patients with mild to moderate endogenous AU to receive difluprednate 0.05% (n = 56) four times daily, alternating with vehicle four times daily, or prednisolone acetate 1% (n = 54) eight times daily. The 14-day treatment period was followed by a 14-day dose-tapering period and a 14-day observation period. The primary efficacy end point was change in anterior chamber cell grade (range, 0 for ≤1 cell to 4 for >50 cells) from baseline to day 14.

Results. At day 14, the mean change in anterior chamber cell grade with difluprednate was noninferior to that with prednisolone acetate (−2.2 vs. −2.0, P = 0.16). The proportions of difluprednate-treated patients versus prednisolone acetate–treated patients demonstrating complete clearing of anterior chamber cells at day 3 were 13.0% vs. 2.1% (P = 0.046) and at day 21 were 73.9% vs. 63.8% (P = 0.013). A significant between-group difference in the mean IOP increase was seen at day 3 (2.5 mm Hg for difluprednate-treated patients and 0.1 mm Hg for prednisolone acetate–treated patients, P = 0.0013) but not at other time points. The mean IOP values in both groups remained less than 21 mm Hg throughout the study.

Conclusions.: Difluprednate 0.05% four times daily is well tolerated and is noninferior to prednisolone acetate 1% eight times daily for the treatment of endogenous AU. (ClinicalTrials.gov number, NCT01201798.)

Introduction

Endogenous anterior uveitis (AU) is a form of uveitis that is not directly caused by an infectious pathogen. It is characterized by intraocular inflammation of the uveal structures anterior to the middle of the vitreous cavity, including iritis, iridocyclitis, and anterior cyclitis. [1–3] The etiology of endogenous AU is incompletely characterized [1,4] but has been associated with systemic diseases such as juvenile idiopathic arthritis, seronegative spondylarthropathies, [5] or Behçet disease, [1,4] as well as abnormalities of the immune system. [2] As with most forms of uveitis, visual morbidity associated with endogenous AU does not usually occur from a single episode; rather, recurrent or prolonged inflammation causes cumulative damage, [6] leading to vision-threatening complications, potential vision loss, decreased quality of life (QoL), and increased socioeconomic cost. [2] Vision-threatening complications of acute or chronic uveitis include cystoid macular edema, [1,6,7] a major cause of vision loss, [2,8] as well as cataract, band keratopathy, glaucoma or ocular hypertension, synechiae formation, pupillary membrane, epiretinal membrane, [1,6,7] subretinal fibrosis, [9] ciliary fibrosis, [10] hypotony, vitreous opacification, and optic nerve edema. [1,6,7]

Given that repeated episodes of uveitis, when untreated or undertreated, may lead to vision impairment, [1] timely treatment is critical. Treatment algorithms typically include topical ophthalmic corticosteroids, [1] with prednisolone acetate 1% being the chief topical

corticosteroid therapy. However, prednisolone acetate 1% usually demands frequent dosing, particularly for severe cases, in which increased administration frequency is required. [1,11] As demonstrated with glaucoma medications, frequent dosing may increase the risk of noncompliance, [12] which may negatively affect the achievement of therapeutic goals. [1] For patients who fail to respond to topical treatment, increased dosage of the topical treatment, periocular (subtenon) or intraocular (intravitreal) corticosteroid injections (triamcinolone), intraocular corticosteroid depot treatment (fluocinolone), or oral corticosteroid therapy may be necessary. However, these alternatives, as well as any prolonged corticosteroid therapy, are often associated with significant adverse effects. [13]

Difluprednate is a prednisolone acetate derivative [14] that is augmented by two fluorinations at carbons 6 and 9, a butyrate group at carbon 17, and an acetic acid group at carbon 21. Relative to its parent molecule, the fluorinations enhance the corticosteroid potency of difluprednate, the butyric acid augments anti-inflammatory activity, and the acetic acid increases penetration. [15] Difluprednate 0.05% has been shown to be effective at reducing inflammation and pain in patients undergoing ocular surgery. [16,17] This study aimed to test the hypothesis that difluprednate 0.05% dosed four times daily is noninferior to prednisolone acetate 1% dosed eight times daily in patients with endogenous AU.

Methods

Study Design

This was a phase III, multicenter, randomized, double-masked, parallel-group, active-controlled noninferiority study conducted at 21 clinical sites throughout the United States between October 2010 and August 2011 in patients with mild to moderate endogenous AU. Eligible patients were randomized in a 1:1 ratio stratified by center, with the use of a block randomization list generated by a computer program for each site, to receive either difluprednate 0.05% (Durezol ophthalmic emulsion; Alcon Research, Ltd., Fort Worth, TX, USA) four times daily, alternating with vehicle four times daily, or prednisolone acetate 1% (Pred Forte ophthalmic suspension; Allergan, Inc., Irvine, CA, USA) eight times daily for 14 days. To maintain masking of treatment allocation, patients assigned to difluprednate 0.05% were given two bottles, one containing difluprednate 0.05% and the other containing vehicle; patients assigned to prednisolone acetate 1% were also given two bottles, both containing prednisolone acetate 1%. Patients were to alternate instillation from each bottle. Because prednisolone acetate 1% requires shaking before use, all patients were instructed to shake all bottles before instillation. The appearance of difluprednate, prednisolone acetate, and vehicle was indistinguishable from one another on inspection (a white, milky liquid). Patients were tapered off the study medication during days 14 to 27 at the discretion of the investigator. On day 14, the first day after completion of the planned treatment course, individuals who responded satisfactorily began graduated tapering of study drug, successively halving the number of doses per day at each step (steps were at days 14–20, days 21–24, and days 25–27). If further tapering was required after day 28, the study drug was to be discontinued and a suitable drug prescribed as deemed appropriate. All patients were observed until day 42.

Patients with increased IOP during the study were allowed an IOP-lowering agent at the discretion of their physician. Concomitant use of mydriatic or cycloplegic drops (administration to be separated from the study medication by at least 10 minutes) to alleviate

photophobia, reduce ciliary spasm pain, or break up synechiae was permitted at the discretion of the investigator.

The study was conducted in accord with the tenets of the Declaration of Helsinki, [18] the protocol was approved by all relevant institutional review boards or ethics committees, and all participants or their legal guardians provided written informed consent. The study was registered at clinicaltrials.gov as NCT01201798.

Patient Selection

Male or female patients 2 years or older with mild to moderate endogenous AU in at least one eye were eligible if the diagnosis was made within 2 weeks of study enrollment and they had at least 11 cells in the anterior chamber according to slitlamp microscopy plus a flare grade of 2 or higher in the eligible eye. Patients were excluded from the study if they had intermediate uveitis, posterior uveitis, panuveitis, corneal abrasion, ulceration, or any confirmed or suspected active viral, bacterial, or fungal keratoconjunctival disease in either eye. Other exclusion criteria included the following: pregnancy or lactation, allergy to other corticosteroids, history of corticosteroid-induced increased IOP, any corticosteroid depot within 6 weeks before start of study drug, known human immunodeficiency virus infection or other immunodeficiency conditions, periocular injection of any corticosteroid solution within 1 week before instillation of study drug, history of glaucoma or clinically significant ocular hypertension documenting an IOP of 21 mm Hg or higher in either eye, any introduction of topical corticosteroid or nonsteroidal anti-inflammatory drug in the eligible eyes within 7 days of study drug, and new administration or change in dosage of any corticosteroid or immunosuppressive drug (including inhaled, nasal, or dermatological corticosteroids) within 2 weeks before study enrollment. The use of contact lenses during the study was prohibited.

End Points and Assessments

The primary efficacy end point was the change from baseline to day 14 in anterior chamber cell grade. The secondary efficacy end points included the following: the mean change from baseline for anterior chamber cell grade and flare grade, as well as total symptom and sign score throughout the study; proportions of patients with anterior chamber cell count of 0, anterior chamber cell grades of 0 and 1 or lower, combined anterior chamber cell count of 5 or lower, and flare grade of 0 at all study visits; and discontinuations resulting from lack of efficacy (defined as treatment failure as assessed at the discretion of the investigator or as an adverse event [AE], with a preferred term of iridocyclitis, iritis, uveitis, or vitreitis). Supportive efficacy end points included QoL and optical coherence tomography (OCT) parameters. The safety end points were AEs, IOP, best-corrected visual acuity (BCVA), extent of exposure to study medication, ophthalmoscopic parameters (fundus assessment and ratio of cup to disc), and slitlamp parameters (lid margins, lids, cornea, sclera, lens, capsule, and conjunctiva).

Study assessments were made on eight visits, at baseline (day 0) and seven postbaseline visits (on days 3, 7, and then every 7 days thereafter through day 42). At each study visit, a slitlamp examination was conducted to assess anterior chamber cell count and grade (range, 0 for ≤1 cell to 4 for >50 cells), [19] anterior chamber flare (range, 0 for none and 4 for severe), and ocular signs (range, 0 for absent to 3 for severe, for synechiae, peripheral anterior synechiae, hypopyon, keratic precipitates, and limbal injection). The BCVA, IOP, and evaluation of

adherence with study medication were documented at each visit. Eye pain, photophobia, blurred vision, and lacrimation were assessed using a visual analog scale (VAS) (range, 0 for absent and 100 for maximal pain and discomfort). The QoL was assessed at baseline and day 42 using the National Eye Institute Visual Function Questionnaire 25 (VFQ-25) and the Work Limitations Questionnaire (WLQ). Optical coherence tomography was repeated only at days 14 and 42. Safety assessments were carried out at all study visits.

Statistical Analysis

The intent-to-treat population comprised all patients who received at least one dose of the allocated study medication. The per-protocol population included patients in the intent-to-treat population who had no major protocol deviation. Major protocol violations were violation of entry criteria, noncompliance (missing ≥24 hours of treatments), and the use of prohibited medications. The per-protocol analyses were performed with visit data excluded when affected by poor compliance or the use of prohibited medications. The per-protocol analyses were performed with last observation carried forward (LOCF) for missing data and for instances when study medication was discontinued or other medication was introduced to manage the condition. The per-protocol population with LOCF was the primary analysis data set for assessing efficacy. Both the per-protocol and intent-to-treat data sets were used for all secondary efficacy end points. Both data sets yielded similar results; for consistency, [19] data from the per-protocol with LOCF analyses are reported herein, and results from the intent-to-treat analyses are included as Supplementary Material. The safety population comprised all patients who received at least one dose of the study medication.

Primary Efficacy Analysis.

To demonstrate noninferiority of difluprednate 0.05% compared with prednisolone acetate 1%, the upper boundary of a two-tailed 95% confidence interval for the difference in the mean change in anterior chamber cell grade from baseline to day 14 (difluprednate minus prednisolone acetate) must be less than the proposed margin of 0.5 U (10% of the five-unit scale). This noninferiority margin was selected based on its use in clinical trials of rimexolone. [20] Analysis of covariance (ANCOVA), with treatment and investigative site as fixed effects and baseline score as a covariate, was used to compare the change from baseline of continuous variables between the difluprednate and prednisolone acetate groups. With 45 evaluable patients per arm and assuming a noninferiority margin of 0.50 and an SD of 0.75, a treatment difference of −0.07 would yield 94% power to demonstrate that difluprednate was noninferior to prednisolone acetate. [19]

Secondary Efficacy Analyses.

Statistical analyses for secondary efficacy outcomes used the same ANCOVA model as for the primary analysis for the mean change from baseline outcomes. χ^2 test was used to compare proportions between treatment groups for the categorical secondary efficacy end points. Analyses were set to a 5% significance level and were two-sided for all tests.

Results

Patient Disposition and Demographics

Of 111 patients randomized, 110 patients were treated with either difluprednate 0.05% or prednisolone acetate 1% and were included in the intent-to-treat and safety populations. One patient randomized to receive difluprednate was treated with prednisolone acetate. This patient was included in the difluprednate group for the intent-to-treat population and in the prednisolone acetate group for the safety population (Fig. 1). The per-protocol LOCF analyses included 46 patients and 47 patients receiving difluprednate and prednisolone acetate, respectively. In total, 9 of 56 patients (16.1%) and 15 of 54 patients (27.8%) in the respective groups discontinued study participation. The most common reason for study discontinuation was treatment failure, which was reported for one patient (1.8%) receiving difluprednate and 8 patients (14.8%) receiving prednisolone acetate (P = 0.013).

Study flow diagram. *One patient was randomized to receive difluprednate 0.05% and was treated with prednisolone acetate 1%. This individual was included in the intent-to-treat population as randomized (difluprednate) and in the safety population as treated (prednisolone acetate) and was excluded from the per-protocol population.

Patient demographic and baseline characteristics were balanced between the two treatment groups (Table 1, Supplementary Table S1). The mean treatment durations were 27.0 days for the difluprednate group and 28.7 days for the prednisolone acetate group (P= 0.25). Baseline anterior chamber cell and flare grades were similar between the two

Discussion

The present study demonstrated that difluprednate 0.05% dosed four times daily was noninferior to prednisolone acetate 1% dosed eight times daily in improving the signs of acute endogenous AU. This conclusion is also supported by the secondary efficacy findings, which showed that difluprednate was associated with similar anterior chamber cell scores throughout the study compared with prednisolone acetate. Comparable improvements in anterior chamber flare grades, symptom and sign scores, QoL, OCT parameters, and BCVA outcomes were also seen in both treatment groups. These results suggested that difluprednate 0.05% four times daily was as effective as prednisolone acetate 1% eight times daily in the treatment of endogenous AU.

Consistent with the results from a previous similarly designed trial by Foster et al., [19] 1.8% of patients in the difluprednate group discontinued the present study owing to treatment failure compared with 14.8% of patients in the prednisolone acetate group (P = 0.01 in both studies). This finding is important because patients not responding to topical treatment commonly require systemic corticosteroid therapy, which is associated with undesirable effects, including hyperglycemia [21] ; furthermore, untreated or undertreated AU may lead to vision-threatening complications and blindness. [1] However, it is acknowledged that treatment failure herein was assessed at the discretion of the investigator.

Ophthalmic medications with a less frequent dosing requirement have been associated with better compliance as demonstrated in therapies for glaucoma [12,22] or allergic conjunctivitis. [23] Similar benefits can be expected with difluprednate 0.05%, which requires dosing at a substantially lower frequency than prednisolone acetate 1%. The formulation

differences between difluprednate and prednisolone acetate may also influence the effectiveness of the two drugs. Notably, prednisolone acetate is a suspension that requires shaking before use, [11] whereas difluprednate emulsion does not. [24] One study [25] found that even with shaking (using a wrist-action mechanical shaker at six cycles per second) only 40% of the prednisolone acetate concentrations were within 15% of the declared concentration compared with 100% for the difluprednate concentrations. Furthermore, prednisolone acetate contains benzalkonium chloride, a preservative that has been associated with allergies, tear film instability, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues in clinical or preclinical investigations. [26] The sorbitol-based preservative in difluprednate has been shown to be less toxic to the corneal epithelium than benzalkonium chloride. [27]

Safety outcomes in the study were within expectations in accord with the package inserts for both study medications. [11,24] Increases in the mean IOP occurred in both groups, which were expected [19,28] ; for example, difluprednate treatment has been shown to be associated with IOP spikes 1 and 7 days after surgery in patients with uncomplicated postoperative cataract. [28] Because inflammation involving the ciliary body may reduce aqueous secretion, resolution of inflammation tends to normalize ciliary function, restoring aqueous secretory capacity and leading to an increase in IOP. [29] Differences between treatment groups in the mean change from baseline IOP were small in magnitude, but five patients in the difluprednate group reported an AE of IOP increase compared with three patients in the prednisolone acetate group. One hypothesis is that difluprednate may be associated with faster recovery of aqueous secretion than prednisolone acetate, thereby explaining at least early differences. It is reassuring that the potentially clinically important criterion increase in IOP (an increase of ≥10 mm Hg that yielded an IOP of ≥21 mm Hg) in this study was infrequent, with similar incidences reported for both groups at any time point. Nevertheless, judicious IOP monitoring with the use of topical corticosteroids (including difluprednate and prednisolone acetate) in patients with uveitis, particularly in those with a history of glaucoma, is recommended. When clinically indicated, prescription of an IOP-lowering topical medication may be appropriate. [30,31] Long-term use of ophthalmic corticosteroids should be also avoided or minimized when possible because it may result in glaucoma, with damage to the optic nerve, visual field defects, VA loss, or cataract formation. [11,24,32,33]

The present study has several limitations. To maintain study masking, the difluprednate group received eight doses per day, four of which were placebo, which may not reflect the real-world use of difluprednate. The study did not include a dosing schedule of prednisolone acetate that is more frequent than every 2 hours, as is sometimes prescribed for severe cases. Owing to the study duration, this study did not include a remission end point, which is commonly defined as uveitis inactivity for a 90-day interval after discontinuing all treatments. [3] Studies with a longer follow-up period may be useful in clarifying between-treatment differences in the duration of remission and other long-term outcomes. Another limitation of this study is that the causes of uveitis among patients, outside of the exclusion criteria, were not addressed. Furthermore, treatment failure was not defined as per protocol and was determined at the discretion of the investigator. Finally, given that the mean baseline anterior chamber cell grade was 2.6 out of a maximum of 4, the difference in the efficacy between difluprednate and prednisolone acetate in the most severe endogenous AU cases is unclear.

In summary, this randomized trial confirmed that difluprednate 0.05% dosed four times daily was noninferior to prednisolone acetate 1% dosed eight times daily for the treatment of endogenous AU during a 42-day observation period; both therapies had comparable safety profiles. Results from this study, together with those reported by Foster et al., [19]suggest that difluprednate is a reasonable alternative approach to prednisolone acetate for resolving and controlling ocular inflammation in patients with endogenous AU.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

BENZALKONIUM CHLORIDE SOLUTION	NF
H.P.M.C E5	USP
SODIUM CHLORIDE	BP/ USP/NF
EDETATE DISODIUM	NF
SODIUM DIHYDROGEN PHOSPHATE	BP
ANHYDROUS DISODIUM HYDROGEN ORTHO PHOSPHATE	BP
HYDROXYPROPYL BETACYCLODEXTRIN	NF
TWEEN – 80 (POLYSORBATE 80)	NF
HYDROCHLORIC ACID	NF
SODIUM HYDROXIDE PELLETS	NF
PURIFIED WATER	BP/IH

6.2 Incompatibilities

~Not applicable. ~

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperature not exceeding 30 degrees C.

Discard the solution if it changes color, turns cloudy, or if it contains particles.

Keep out of the reach of children.

Prescription only Medicine.

6.5 Nature and contents of container

The liquid is filled in a multi dose container, and contain Benzalkonium Chloride Solution, H.P.M.C E5, Edetate Disodium, Sodium Chloride, and Sodium Dihydrogen Phosphate, Anhydrous Disodium hydrogen Phosphate, Hydroxypropyl Betacyclodextrine, Tween-80, Hydrochloric Acid and Sodium Hydroxide Pellets for pH adjustment.

6.6 Special precaution for disposal of a used medicinal product or waste materials derived such medicinal product and other handling of the product

No special requirements