PRODUCT MONOGRAPH

HydroVal

(Hydrocortisone Valerate USP)

Cream & Ointment 0.2 %

Topical Corticosteroid

TaroPharma
A Division of Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario
L6T 1C1

Revision Date:
July 25, 2008

Control # 120675

PRODUCT MONOGRAPH

HydroVal

Cream & Ointment 0.2 %

(Hydrocortisone Valerate Cream, USP)
(Hydrocortisone Valerate Ointment, USP)

Topical Corticosteroid

ACTIONS AND CLINICAL PHARMACOLOGY

HydroVal 0.2% (hydrocortisone valerate) cream and ointment are moderately potent non-fluorinated, topical corticosteroids. Topical corticosteroids are synthetic derivatives of cortisone which are effective when applied locally to control many types of inflammatory, allergic and pruritic dermatoses. Modifications to the chemical structure such as fluorination, generally enhances both anti-inflammatory activity and increases the likelihood of adverse effects. The mechanism of anti-inflammatory activity of topical corticosteroids is generally unclear. However, corticosteroids are thought to induce phospholipase A2 inhibitor proteins, preventing arachidonic acid release and the biosynthesis of potent mediators of inflammation.

Topical corticosteroids are primarily effective because of their anti-inflammatory, anti-pruritic and vasoconstrictive actions.

Topical absorption of corticosteroids follow the same pharmacologic fate as systemically administered doses: corticosteroids in the circulation are bound to plasma proteins, although the fluorinated compounds are bound to a lesser degree, accounting for their increased potency compared to natural corticosteroids.

It is generally known that steroid hormones are metabolized predominantly in the liver and to a lesser extent in the kidney, intestines, spleen, muscles and other tissues and then excreted in the urine as conjugates.

INDICATIONS AND CLINICAL USE

HydroVal 0.2% (hydrocortisone valerate) cream and ointment are indicated for topical therapy of acute and chronic corticosteroid responsive dermatoses, where an anti-inflammatory, anti-allergenic and antipruritic activity is required in the topical management of these conditions.

CONTRAINDICATIONS

HydroVal 0.2% (hydrocortisone valerate) cream and ointment are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation. HydroVal 0.2% (hydrocortisone valerate) cream and ointment should not be used in bacterial/fungal skin infections, tuberculosis

of the skin, syphilitic skin infections, chicken pox, eruptions following vaccinations and viral diseases of the skin in general. Not for ophthalmic use.

WARNINGS

When used under occlusive dressing, over extensive areas, or on the face, scalp, axillae and scrotum, sufficient absorption may occur giving rise to adrenal suppression and other systemic effects.

PRECAUTIONS

General

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycaemia and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids.

Conditions which augment systemic absorption include application of the more potent steroids, use over large surface areas, prolonged use, occlusive dressings. Patients receiving a large dose of potent topical steroids to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACT stimulation test or

other recognized/validated test. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur requiring supplemental systemic corticosteroids. Occlusive dressings should not be applied if body temperature is elevated.

To minimize systemic absorption when long-term therapy or large surface area for treatment is likely, periodic interruption of treatment or treatment of one area of the body at a time should be considered.

Children may be more susceptible to systemic toxicity from equivalent doses due to larger skin surface to body mass ratios (see Precautions- Pediatric Use).

Topical corticosteroids, particularly the more potent ones, should be used with caution on lesions close to the eye because systemic absorption may cause increased intra ocular pressure, glaucoma or cataracts.

Prolonged use of topical corticosteroid preparations may produce striae or atrophy of the skin or sub-cutaneous tissue. Topical corticosteroids should be

used with caution on lesions of the face, groin and axillae as these areas are more prone to atrophic changes than other areas of the body. Frequent observation is important if these areas are to be treated. If skin atrophy is observed, treatment should be discontinued.

If irritation develops, HydroVal (hydrocortisone valerate) should be discontinued and appropriate therapy instituted. Allergic contact dermatitis from corticosteroids is usually diagnosed by observing 'failure to heal' rather than clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

Suitable precautions should be taken when using topical corticosteroids in patients with stasis dermatitis and other skin diseases with impaired circulation.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favourable response does not occur promptly, use of HydroVal (hydrocortisone valerate) cream or ointment should be discontinued until the infection has been adequately controlled.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Use in Pregnancy

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage. HydroVal (hydrocortisone valerate) cream or ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, particularly in the first trimester of pregnancy. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

Lactating/Nursing Mothers

Systemically administered corticosteroids are secreted into human milk and could suppress growth, interfere with endogenous corticosteroid production or cause untoward effects. Caution should be exercised when HydroVal (hydrocortisone valerate) cream or ointment is administered to a nursing mother.

Pediatric Use

Safety and effectiveness of HydroVal (hydrocortisone valerate) in children and infants have not been established. Because of the higher ratio of skin surface area to body mass, children are at a higher risk than adults for HPA axis suppression when treated with topical corticosteroids. They are also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effect including striae have been reported with use of topical corticosteroids in infants and children. HPA axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include: linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACT stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilloedema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

Carcinogenesis, Mutagenicity, Reproduction

Long-term animal studies have not been performed to evaluate the carcinogenic or mutagenic potential of hydrocortisone valerate or its effects on reproduction.

ADVERSE REACTIONS

The following local adverse reactions have been reported with the use of topical corticosteroids and may occur more frequently with the use of occlusive dressings. These reactions are listed in decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae and miliaria. In addition, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

Adrenal suppression has occurred with prolonged use of large doses of topical corticosteroids, particularly under occlusion due to increased percutaneous absorption.

Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

OVERDOSE: SYMPTOMS AND TREATMENT

Topically applied HydroVal (hydrocortisone valerate) cream and ointment can be absorbed systemically. Percutaneous absorption is enhanced when large amounts of corticosteroids are applied, when used under occlusive dressing or when used chronically. Toxic effects of hypercorticism and adrenal suppression may appear. Should toxic effects occur, the dosage of HydroVal (hydrocortisone valerate) cream and ointment should be discontinued slowly, consistent with accepted procedures for discontinuation of chronic steroid therapy. The restoration of hypothalamic-pituitary axis may be slow; during periods of pronounced physical stress (severe infections, trauma, surgery); a supplement with systemic steroids may need to be considered.

Toxic effect may include ecchymosis of skin, peptic ulceration, hypertension, aggravation of infection, hirsutism, acne, edema and muscle weakness due to protein depletion. Treatment of a patient with systemic toxic manifestations consists of assuring and maintaining a patent airway and supporting ventilation using oxygen and assisted or controlled respiration as required. This usually will be sufficient in the management of most reactions. Should circulatory depression occur, vasopressors and i.v. fluids may be used. Should a convulsion persist despite oxygen therapy, small increments of ultra-short acting barbiturate

(pentobarbital or secobarbital) may be given i.v. Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions.

DOSAGE AND ADMINISTRATION

Apply a small amount of HydroVal 0.2% (hydrocortisone valerate) cream or ointment to the affected areas of skin 2 to 3 times daily as needed. Rub in gently and completely. If a symptomatic response is not noted within a few days to a week, the local applications of corticosteroid should be discontinued and the patient re-evaluated. Therapy should be discontinued as soon as lesions heal.

It is recommended that HydroVal 0.2% (hydrocortisone valerate) cream and ointment not be used under occlusive dressings unless directed by a physician.

PATIENT INFORMATION

HydroVal cream and ointment are indicated for the treatment of acute and chronic corticosteroid responsive dermatoses, where an anti-inflammatory, anti-allergenic and antipruritic activity is required in the topical management of these conditions.

This medication is to be used as directed by the physician. It is only for external use. Avoid contact with eyes.

This medication should not be used for any disorder other than that for which it is prescribed.

Do not use occlusive wrapping/bandages on treated sites unless directed by a physician.

If you are pregnant, intend to become pregnant or are breast feeding or intend to breast feed, inform your physician.

Inform your physician of prior or current use of corticosteroids for treatment of skin disorders, allergic reactions, arthritis or asthma. In particular, tell your physician if you have developed an allergy or intolerance to such medicine. Also inform your physician of allergies to other substances such as foods, dyes etc.

Do not exceed the prescribed dose.

Contact your physician if there is no improvement in your condition within 1 week.

Report any signs of local adverse reactions to your physician.

Do not have any immunizations without your doctor’s approval if you are using this medication.

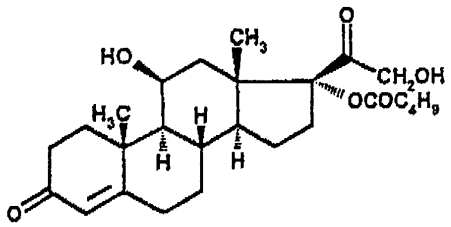
PHARMACEUTICAL INFORMATION

a) Drug Substance

Proper Name: Hydrocortisone Valerate USP

Chemical Name: Pregn-4-ene-3,20-dione, 11, 21-dihydroxy-17-[(1-oxopentyl)oxy)-, (11β).

Structural Formula:



Molecular Weight: 446.6 Molecular formula: $C_{26}H_{38}O_6$

Description: Hydrocortisone-17-Valerate is a white, odourless crystalline powder. It is soluble in ethanol, acetone, propylene glycol, PEG 400, castor oil,

dioxane and chloroform, but is insoluble in water and mineral oil.

b) Composition: *Cream:* Each 15, 45 and 60 g tube and 500 g jar of cream contains: Hydrocortisone -17-Valerate 0.2%.

Nonmedical ingredients: Purified Water, Carbomer 940, Sodium Phosphate, Dibasic, Sodium Lauryl Sulphate, Propylene Glycol, Methylparaben, White Petrolatum, Stearyl Alcohol, Steareth-2, Steareth-100.

Ointment: Each 15, and 60 g tube of ointment contains Hydrocortisone-17 valerate 0.2%.

Nonmedical ingredients: Purified Water, Carbomer 934P, Sodium Phosphate, Dibasic, Sodium Lauryl Sulphate, Propylene Glycol, Methylparaben, White Petrolatum, Mineral Oil, Stearyl Alcohol, Steareth-2, Steareth-100.

c) Stability and Storage Conditions:

Store at controlled room temperature (15-25˚C).

AVAILABILITY AND DOSAGE FORMS

HydroVal Cream, 0.2% is available in tubes of 15, 45, and 60 grams and in a jar of 500 grams.

HydroVal Ointment, 0.2% is available in tubes of 15 and 60 grams.

PHARMACOLOGY

When studied in the cotton pellet granuloma assay in rats, croton oil induced mouse ear inflammation assay, and Carrageenin induced rat paw edema assay, Hydrocortisone-17-valerate 0.2% demonstrated anti-inflammatory activity. Other glucocorticoid activities such as gluconeogenesis were also demonstrated in mice. Hydrocortisone-17-valerate did not show unexpected pharmacological activities as a topical anti-inflammatory corticosteroid.

Studies conducted in healthy adult volunteers illustrated that 0.2 % Hydrocortisone-17-Valerate cream and ointment have minimal primary irritant and contact sensitization potential. Adrenal suppression studies with the cream indicated that any observed reduction in pituitary-adrenal function was rapidly reversible.

Vasoconstrictor Tests

Vasoconstrictor assay has proved to be a reliable human bioassay for the screening of compounds with topical corticosteroid activity, and for the comparative evaluation of biologic effects relative to existing standards.

Although the results of this standardized assay method cannot be directly equated with topical efficacy in dermatologic therapy, they appear to have definite predictive value, and correlate well with clinical activity and potency. According to McKenzie, "the most powerful vasoconstrictors are those substances which clinical studies have shown to be the most effective topical anti-inflammatory agents".

A one-period, randomized, study was performed with 43 pre-screened, asymptomatic, female subjects to compare the bioavailability of HydroVal (hydrocortisone valerate) Cream 0.2%, with that Westcort® (hydrocortisone valerate) Cream 0.2% (manufactured by Westwood-Squibb). The degree of vasoconstriction was determined both by visual assessment and with a Chromameter. Statistical analysis was performed on the subjects that met the predetermined qualification criteria. A total of 30 of the 43 subjects met the qualifying criteria for the visual result and 26 met the criteria for the Chromameter results. Table 1 below, summarizes the results of this study. Locke's Method for calculating confidence intervals was applied to the visual

and Chromameter area results from those subjects included in the analysis. HydroVal (hydrocortisone valerate) Cream 0.2% was found to bioequivalent to Westcort® (hydrocortisone valerate) Cream 0.2%.

Table 1: Mean results for visual and Chromameter evaluation of HydroVal cream vs. Westcort cream using Locke's Method for calculating confidence intervals.

Summary Table of the Comparative Bioavailability Data
Hydrocortisone Valerate Creams
(10 µL x 2.0 mg/g)
From measured data
Arithmetic Means

Parameter	**N (number of subjects)**	**Means**		**Ratio (%)** (TaroPharma/ Reference x 100)	**90% Confidence Interval (confidence interval on the ratio)**	
		Test HydroVal Lot S133-5592	**Reference *Westcort Lot 5270**		**Lower (%)**	**Upper (%)**
Visual	30	23.35	26.83	87.0	79.2	94.6
Chromameter	26	17.56	18.33	95.8	81.4	112.7

*Westcort Cream 0.2%, manufactured by Westwood-Squibb

A one-period, randomized, study was performed with 40 pre-screened, asymptomatic, female subjects to compare the bioavailability of HydroVal (hydrocortisone valerate) Ointment 0.2%, with that of Westcort® (hydrocortisone valerate) Ointment 0.2% (manufactured by Westwood-Squibb). The degree of vasoconstriction was determined both by visual assessment and with a Chromameter. Statistical analysis was performed on the subjects that met the predetermined qualification criteria. A total of 38 of the 39 subjects who completed the study, met the qualifying criteria for the visual result and 34 met

the criteria for the Chromameter results. Table 2 below, summarizes the results of this study. Locke's Method for calculating confidence intervals was applied to the visual and Chromameter area results from those subjects included in the analysis. HydroVal (hydrocortisone valerate) Ointment 0.2% was found to bioequivalent to Westcort® (hydrocortisone valerate) Ointment 0.2%.

Table 2: Mean results for visual and Chromameter evaluation of HydroVal ointment vs. Westcort ointment using Locke's Method for calculating confidence intervals.

Summary Table of the Comparative Bioavailability Data
Hydrocortisone Valerate Ointments
(10 µL x 2.0 mg/g)
From measured data
Arithmetic Means

Parameter	N (number of subjects)	Means		Ratio (%) (TaroPharma/ Reference x 100)	90% Confidence Interval (confidence interval on the ratio)	
		Test HydroVal Lot S139-5590	Reference *Westcort Lot 5335		Lower (%)	Upper (%)
Visual	38	27.63	33.79	81.8	76.1	87.2
Chromameter	34	27.08	29.59	91.5	83.6	100.4

*Westcort Ointment 0.2%, manufactured by Westwood-Squibb

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. They are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

TOXICOLOGY

Animal Studies: Toxicological studies involving oral and dermal dosage of rats, mice, dogs and rabbits, revealed no long-lasting toxicity or irritation resulting from dosage levels equivalent to those intended for use in man. Hydrocortisone-17-valerate has a very low acute toxicity potential, in mice LD_{50} of 1600 mg/kg orally; in rats of 1600 mg/kg orally, Hydrocortisone- 17-valerate (0.2% cream) orally in mice and rat was 20 mL/kg, and in dog 6 mL/kg. Percutaneous dosage in rabbit resulted in an LD_{50} of 10 mL/kg. Thirty day subacute topical application of Hydrocortisone-17-valerate in rabbits resulted in changes expected from the chronic administration of steroids in animals, at the end of the 2-week recovery period, all changes had returned to normal.

BIBLIOGRAPHY

l. McKenzie, A.W. and Stoughton, R.B.. Arch. Dermatol. 86:608-610,1962.

2. Feldmann, R.J. and Maibach, H.I.. Arch. Dermatol. 91:661-666,1965.

3. Monro, D.D.. Br. J. Dermatol. 94 (Supplement 12):67-76, 1976.

4. McKenzie, SEA., Selley, J.A., and Agnew, J.E.. Arch. Dis. Child.50:89406,1975.

5. Katz, F.H. and Duncan, B.R.. N. Eng. J. Med.293:1154 1975.

6. Hendhkse, J.C.M. and Moolenaar, A.J.. Dermatologica 144:179-186,1972.

7. Westwood Pharmaceuticals. Product Monograph: WESTCORT. March 30, 1983.