PRESCRIBING INFORMATION

PrUREMOL® HC

Hydrocortisone acetate USP 1% (w/w)
and Urea USP 10% (w/w) Cream

Hydrocortisone acetate USP 1% (w/v)
and Urea USP 10% (w/v) Lotion

Topical Corticosteroid – Emollient

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Date of Revision:
April 16, 2014

Control Number: 170409

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Topical Corticosteroid

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical use	Cream, 1% w/w Hydrocortisone acetate USP and 10% w/w Urea USP Lotion, 1% w/v Hydrocortisone acetate USP and 10% w/v Urea USP	Preservative: Germaben II For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

INDICATIONS AND CLINICAL USE

UREMOL® HC Cream and Lotion (hydrocortisone acetate USP and urea USP) are indicated for topical therapy of corticosteroid responsive dermatoses with dry skin conditions for a maximum duration of 4 weeks, where an anti-inflammatory and antipruritic activity is required in the topical management of these conditions.

Geriatrics (> 65 years of age): Safety and effectiveness of UREMOL® HC in geriatric patients over 65 years of age have not been established. Some published studies of 1% hydrocortisone creams have reported that clinical outcomes in geriatric patients over 65 years of age were consistent with those of the general adult population (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (> 65 years of age)).

Pediatrics (<18 years of age): UREMOL® HC is not recommended for use in children under 2 years of age. Elevated plasma urea levels have been observed in neonates following topical exposure to urea-based creams. Safety and effectiveness of UREMOL® HC in pediatric patients less than 18 years of age have not been established. Some published studies of 1% hydrocortisone creams have reported that clinical outcomes in pediatric patients less than 18 years of age were consistent with those of the general adult population (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (<18 years of age)).

CONTRAINDICATIONS

- Patients who are hypersensitive to these drugs (hydrocortisone and urea) or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the PRESCRIBING INFORMATION.
- Patients who are hypersensitive to other corticosteroids.
- Patients with bacterial, tubercular, or fungal infections involving the skin, viral diseases (such as herpes simplex, chicken pox and vaccinia), parasitic infections, skin manifestations relating to tuberculosis or syphilis, eruptions following vaccinations, rosacea, acne vulgaris, and pruritus without inflammation.
- Topical application to the eye.

WARNINGS AND PRECAUTIONS

General

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

UREMOL® HC Cream and Lotion should not be used under occlusion, due to increased risk of systemic exposure and infection. When used under occlusive dressing, over extensive areas, on the face, scalp, axillae or scrotum, sufficient absorption may occur to result in adrenal suppression and other systemic effects (see WARNINGS AND PRECAUTIONS – Endocrine and Metabolism, Immune and Ophthalmologic).

Keep UREMOL® HC Cream and Lotion away from the eyes and all mucous membranes. In case of contact, wash with water.

UREMOL® HC Cream and Lotion are for external use only. Avoid use on open wounds.

Cardiovascular

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

Use of corticosteroids around chronic leg ulcers may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

Endocrine and Metabolism

Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical corticosteroids. Hyperglycemia and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids (see ADVERSE REACTIONS).

Conditions which augment systemic absorption include the formulation and potency of the topical corticosteroid, the application of topical corticosteroids over large body surface areas, application to intertriginous areas (such as the axillae), frequency of application, prolonged use, or the use of occlusive dressings. Other risk factors for increased systemic effects include increasing hydration of the stratum corneum, use on thin skin areas (such as the face), and use on broken skin or in conditions where the skin barrier may be impaired. Additionally, urea increases the absorption of hydrocortisone in UREMOL® HC (see ACTION AND CLINICAL PHARMACOLOGY).

If patients must be treated over large body surface areas, they should be evaluated periodically for evidence of HPA axis suppression (see WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests). If HPA axis suppression or Cushing's syndrome is observed, an attempt should be made to withdraw the drug by reducing the frequency of application. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency (see ADVERSE REACTIONS).

Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic corticosteroid supplementation, see the prescribing information for those products.

Pediatric patients may absorb larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity from equivalent doses because of their larger skin surface to body mass ratios as compared with adult patients (see WARNINGS AND PRECAUTIONS – Special Populations, Pediatrics).

Immune

Topical corticosteroids may increase the risk of infections including aggravation of cutaneous infection, masked infection and secondary infections. In particular, bacterial infection is encouraged by the warm, moist conditions within skin-fold areas, or caused by occlusive dressings. If concomitant skin infections develop, UREMOL® HC should be discontinued and antimicrobial therapy should be administered.

Ophthalmologic

Topical corticosteroids should be used with caution on lesions close to the eye because systemic absorption may cause increased intraocular pressure, cataract, or glaucoma.

Sensitivity

Local hypersensitivity reactions (see ADVERSE REACTIONS) may resemble symptoms of the condition under treatment. If hypersensitivity reactions occur, UREMOL® HC should be discontinued and appropriate therapy should be initiated.

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noticing a clinical exacerbation. Such an observation should be corroborated with appropriate diagnostic patch testing.

Skin

If significant irritation develops, UREMOL® HC should be discontinued and appropriate therapy should be instituted.

Prolonged use of topical corticosteroid preparations may produce striae or atrophy of the skin or subcutaneous 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.

Due to the hypertonicity of the urea formulations, stinging may occur when applied to irritated or fissured skin. This is a transitory effect and usually disappears after several applications. If irritation worsens or persists, UREMOL® HC should be discontinued temporarily.

UREMOL® HC Cream contains propylene glycol which may cause skin reactions, and cetyl alcohol which may cause local skin reactions (e.g. contact dermatitis) and skin irritation.

Special Populations

Pregnant Women: Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development (see TOXICOLOGY). Subcutaneous administration of hydrocortisone to mice at doses of ≥30 mg/kg/day, to rabbits at a dose of 675 µg/kg/day, and the administration of a single intramuscular injection of ≥25 mg to hamsters during pregnancy produced fetal abnormalities including cleft palate. The relevance of this finding to human beings has not been established.

There are no clinical data on the use of topical urea in pregnant women. Studies in animals do not indicate harmful effects from topical administration of urea with respect to reproductive toxicity and developmental toxicity (see TOXICOLOGY).

There are no adequate and well-controlled studies of UREMOL® HC in pregnant women. Administration of UREMOL® HC during pregnancy should only be considered if the expected benefit to the mother outweighs the potential risk to the fetus. The minimum quantity should be used for the minimum duration. Pregnant women should seek medical advice before using topical UREMOL® HC.

Nursing Mothers: The safe use of topical corticosteroids during lactation has not been established.

It is unknown whether topically applied urea is excreted in human breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

Because many drugs are excreted in human milk, caution should be exercised when UREMOL® HC is administered to a nursing woman. Nursing women should seek medical advice before using UREMOL® HC. Administration of UREMOL® HC during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.

If used during lactation, UREMOL® HC should not be applied to the breasts to avoid accidental ingestion by the infant.

Pediatrics (<18 years of age): The safety of UREMOL® HC has not been studied in pediatric patients. UREMOL® HC is not recommended for use in children under 2 years of age. Elevated plasma urea levels have been observed in neonates following topical exposure to urea-based creams.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during and/or after withdrawal of treatment.

Adverse effects including striae have been reported with the use of topical corticosteroids in infants and children. HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Chronic corticosteroid therapy may interfere with the growth and development of children.

There are no adequate and well-controlled studies of UREMOL® HC in pediatric patients. Some published studies of 1% hydrocortisone creams have reported that clinical outcomes in pediatric patients less than 18 years of age were consistent with those of the general adult population.[3, 5, 9, 16] Administration of topical corticosteroids to children under 18 years of age should be limited to the least amount and for the shortest duration compatible with an effective therapeutic regimen (see DOSAGE AND ADMINISTRATION).

Geriatrics (>65 years of age): The safety of UREMOL® HC has not been studied in geriatric patients.

In general, topical corticosteroids should be used cautiously in elderly patients, reflecting their increased skin fragility and greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant disease or other drug therapy. The greater frequency of decreased hepatic or renal function in the elderly may delay elimination if systemic absorption occurs.

There are no adequate and well-controlled studies of UREMOL® HC in geriatric patients. Some published studies of 1% hydrocortisone creams have reported that clinical outcomes in geriatric patients over 65 years of age were consistent with those of the general adult population.[3, 9, 15, 16] For geriatric patients over 65 years of age, the minimum quantity should be used for the minimum duration (see DOSAGE AND ADMINISTRATION).

Patients with renal / hepatic impairment: The safety of UREMOL® HC has not been studied in patients with renal or hepatic impairment.

In case of systemic absorption, metabolism and elimination may be delayed leading to increased risk of systemic toxicity.

There are no adequate and well controlled studies of UREMOL® HC in patients with renal or hepatic impairment. For patients with renal or hepatic impairment, the minimum quantity should be used for the minimum duration (see DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

The cosyntropin (ACTH $_{1-24}$) stimulation test may be helpful in evaluating patients for HPA axis suppression.

ADVERSE REACTIONS

Post-Marketing Adverse Drug Reactions

The following adverse reactions have been identified during the post-approval use of UREMOL® HC. Because these 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.

Endocrine Disorders: Hypothalamic-pituitary adrenal (HPA) axis suppression, cushingoid features (e.g. moon face, central obesity), increased weight /obesity, delayed weight gain/growth retardation in children, decreased endogenous cortisol levels, hyperglycemia/glucosuria, hypertension, osteoporosis, and steroid withdrawal syndrome.

Eye Disorders: Cataract, glaucoma.

General Disorders and Administrative Site Reactions: Application site irritation/pain.

Immune System Disorders: Local hypersensitivity.

Infections and Infestations: Secondary infection.

Skin and Subcutaneous Tissue Disorders: Contact dermatitis /dermatitis, erythema, rash, urticaria, pruritus, skin burning, skin pain, skin exfoliation, skin atrophy*, atrophy of subcutaneous tissues, skin dryness*, skin striae*, change in pigmentation*, hypertrichosis, telangiectasia*, and exacerbation of underlying symptoms. The following have been observed with the use of occlusive dressings: pustules, miliaria, folliculitis and pyoderma.

*****Skin features secondary to local and/or systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression.

DRUG INTERACTIONS

Overview

No clinical trials were specifically designed to assess potential drug-drug, drug-food, drug-herb, or drug-laboratory interactions with UREMOL® HC Cream or Lotion.

Co-administered drugs that can inhibit CYP3A4 (e.g., ritonavir, itraconazole) have been shown to inhibit the metabolism of corticosteroids leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP3A4 inhibitor.

When urea is co-administered with other topically applied medicines, it may result in their increased absorption through the skin barrier.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients/caregivers should be instructed to use the minimum quantity of UREMOL® HC for the shortest duration of time necessary to achieve the desired therapeutic benefit because of the potential for corticosteroids to suppress the hypothalamic-pituitary-adrenal (HPA) axis and cause skin atrophy (see WARNINGS AND PRECAUTIONS).
- If the condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated.
- UREMOL® HC is for topical use only and not for ophthalmic use.
- Pediatric patients may be more susceptible to local and systemic toxicity from equivalent doses of topical corticosteroids because of their larger skin surface to body weight ratios, and may require shorter courses of treatment than adults.
- Geriatric patients may be more susceptible to percutaneous absorption and the potential effects of systemic absorption. The greater frequency of decreased hepatic or renal function in the elderly may delay elimination if systemic absorption occurs.
- The affected area should be clean and dry.
- Excess product should not be returned to the container, since it may cause contamination.

Recommended Dose and Dosage Adjustment

A thin layer should be applied to affected areas once or twice a day for a maximum of 4 weeks. If the condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated.

Avoid abrupt discontinuation of topical corticosteroids when control is achieved, as rebound of pre-existing dermatoses can occur. Continue an emollient as maintenance therapy.

Pediatrics (<18 years of age): Care should be taken when using UREMOL® HC in pediatric patients. Use in children should be under the supervision of an adult. The safety and efficacy of urea have not been established in children under 2 years of age. The minimum quantity should be used for the shortest duration to achieve the desired therapeutic benefit (see WARNINGS AND PRECAUTIONS – Special Populations, Pediatrics (< 18 years of age)).

Geriatrics (>65 years of age): UREMOL® HC should be used with caution in geriatric patients due to increased risk of renal or hepatic impairment in this population. The minimum quantity should be used for the shortest duration to achieve the desired therapeutic benefit (see WARNINGS AND PRECAUTIONS — Special Populations, Geriatrics (> 65 years of age)).

Renal/Hepatic Impairment: In patients with renal or hepatic impairment, the minimum quantity should be used for the shortest duration to achieve the desired therapeutic benefit (see WARNINGS AND PRECAUTIONS — Special Populations, Patients with renal / hepatic impairment).

Missed Dose

In the event of missed dose, UREMOL® HC Cream or Lotion should be applied as soon as possible after the missed dose is remembered. If this is close to the scheduled application time or the next dose, the patient should wait and apply the next scheduled dose. The usual schedule should be resumed thereafter.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see WARNINGS AND PRECAUTIONS). Excessive prolonged use or misuse may suppress hypothalamic-pituitary-adrenal (HPA) axis function, resulting in secondary adrenal insufficiency. Excessive topical application of urea may result in severe skin irritation. If symptoms of HPA axis suppression occur, UREMOL® HC should be withdrawn gradually by reducing the frequency of application. Further management should be as clinically indicated. If toxic effects occur, UREMOL® HC treatment should be discontinued and symptomatic therapy should be administered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

UREMOL® HC Cream and Lotion contain hydrocortisone, which belongs to a class of topical drugs called topical corticosteroids. It is considered to be a mild or low potency corticosteroid. Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of anti-inflammatory activity of topical corticosteroids is unclear. However,

corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostagladins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

UREMOL® HC Cream and Lotion contain urea, which is a naturally occurring degradation product of proteins in humans. On the surface of the skin, urea binds water and increases the water substantivity of the stratum corneum. Urea also gently dissolves the intercellular matrix which results in loosening the stratum corneum of skin and shedding scaly skin at regular intervals, thereby softening hyperkeratotic areas of the skin. An 8 molar solution of urea solubilizes the fibrous protein keratin. It breaks down proteins by breaking the hydrogen bonding system rather than by denaturing. After *in vivo* application of urea preparation, the removed stratum corneum retains more water than the stratum corneum treated with base

Pharmacodynamics

The Pharmacodynamics of UREMOL® HC Cream and Lotion have not been specifically investigated in any clinical studies. Topical corticosteroids have anti-inflammatory, antipruritic, and vasoconstrictive properties.

Urea, in combination with other topically applied medicines, can increase their absorption and accelerates penetration of topical preparations (see WARNINGS AND PRECAUTIONS, Endocrine). This is thought to be due to urea's ability to increase the hydration of the stratum corneum and thus improve the absorption of other medicines. When urea is loosely bound to an insoluble matrix which consists largely of an inert polysaccharide material it is stable in that form and readily diffuses into the skin where it raises the water holding capacity of the epidermis.

Pharmacokinetics

The pharmacokinetics of UREMOL® HC Cream and Lotion (absorption, distribution, excretion, and metabolism) have not been specifically investigated in any clinical studies. Pharmacokinetic properties of the drug class of topically applied corticosteroids remain incompletely understood.

Absorption: Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the product formulation, potency, vehicle, frequency and duration of application, as well as the integrity of the epidermal barrier, skin thickness, application to intertriginous areas (such as the axillae) and to large skin surface areas. Occlusion, hydration of the stratum corneum, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.

After topical application of urea, only a small percentage of the active ingredient permeates epidermis and dermis. In an *in vitro* study using human abdominal skin, approximately 9.5 % of the topically applied dose of urea was absorbed percutaneously. The amount of urea absorbed increased approximately 7 fold to 67.9 % when applied to damaged human abdominal skin.

Distribution: The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary because circulating levels are well below the level of detection.

Topically applied urea is unlikely to reach the systemic circulation in measurable quantities. If very small quantities of urea are absorbed, they will be distributed predominantly in the extracellular space such as blood.

Metabolism: Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolized, primarily in the liver.

Urea is a naturally occurring degradation product of proteins in humans. Topically applied urea is not metabolized further before excretion.

Excretion: Topical corticosteroids are excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Topically applied urea is excreted unchanged primarily via urine and, to a lesser extent, via sweat. Urea undergoes glomerular filtration in the kidneys. Up to 50 % of the filtered urea is reabsorbed in the proximal tubule.

STORAGE AND STABILITY

Store between 15ºC and 30ºC. Keep out of direct sunlight. Keep out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

UREMOL® HC Cream contains hydrocortisone acetate USP 1% w/w and urea USP 10% w/w in an aqueous emollient hydrating base composed of propylene glycol, capric/caprylic triglyceride, isopropyl myristate, xanthan gum, sodium lauryl sulfate, edetate disodium, Ceteareth-12, Ceteareth-20, glyceryl stearate, octyldodecanol, potassium phosphate monobasic, sodium phosphate dibasic, cetyl alcohol, lanolin alcohol/mineral oil, purified water; and Germaben II (parabens) as preservative.

UREMOL® HC lotion contains hydrocortisone acetate USP 1% w/v and urea USP 10% w/v in an aqueous emollient hydrating base composed of edetate disodium, sodium phosphate dibasic anyhydrous, citric acid anhydrous, xanthan gum, glycerin, Ceteareth-12, Ceteareth-20, glyceryl stearate, capric/caprylic triglyceride, octyldodecanol, acetylated lanolin alcohol/cetyl stearate, isopropyl myristate, purified water; and Germaben II (parabens) as preservative.

UREMOL® HC Cream is available in 50 g plastic tube and 225 g jar.
UREMOL® HC Lotion is available in a 150 mL plastic tube.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance: Hydrocortisone Acetate

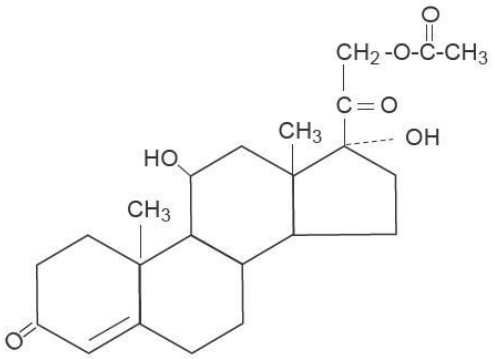
Common name: Hydrocortisone Acetate USP

Chemical name: 11β,17,21-Trihydroxypregn-4-ene-3,20-dione,21 acetate

Molecular formula: $C_{23}H_{32}O_6$

Molecular mass: 404.51

Structural formula:



Physicochemical properties: White to practically white, odourless, crystalline powder.
Insoluble in water; slightly soluble in alcohol and in chloroform.

Melting point: 220°C

Drug Substance: Urea

Common name: Urea USP

Chemical name: Carbamide

Molecular formula: CH_4N_2O

Molecular mass: 60.06

Physicochemical properties:	Colourless to white, prismatic crystals, or white, crystalline powder. Is practically odourless, but may gradually develop a slight odour of ammonia upon long standing. Its solutions are neutral to litmus. Freely soluble in water and in boiling alcohol; soluble in alcohol; practically insoluble in chloroform and in ether.

TOXICOLOGY

A Primary Dermal Irritation Study was conducted in order to determine the degree of dermal irritation resulting from administration of the preparation to abraded and intact skin sites on albino rabbits. Observations of irritations were made according to the method of Draize at 24, 72 hours and daily thereafter, for a period of 7 days post application. A primary dermal irritation index was derived for each animal at each observation period. UREMOL® HC cream applied as a patch application to abraded and intact skin elicited a very mild dermal irritation. Within 24 hours of dosing, the lesion was characterized by slight erythema and/or edema. While all signs of edema had disappeared by day 3 of the study, very slight erythema was generally visible till around day 4. Exposure to the test article subsequent to abrasion of the skin does appear to slightly increase the irritation and delay the healing process. It was concluded that UREMOL® HC (hydrocortisone acetate and urea) is a very mild dermal irritant in albino rabbits.

Carcinogenesis

Long term animal studies have not been performed to evaluate the carcinogenic potential of topical corticosteroids. Subcutaneous injection of hydrocortisone at 50 mg/kg once per week for 52 weeks was not carcinogenic in male rats.[17]

The carcinogenic potential of topically applied urea has not been evaluated. However, carcinogenicity studies conducted with urea in Fisher 344 rats and C57B1/6 mice fed diets containing up to 4.5% urea demonstrated no evidence of carcinogenic risk.

Genotoxicity

Hydrocortisone was not mutagenic in a bacterial mutagenicity assay (*Salmonella typhimurium*) in the absence or presence of metabolic activation, and was not genotoxic in an unscheduled DNA synthesis (UDS) assay in rat primary hepatocytes. Hydrocortisone was genotoxic in a chromosome aberration assay in human lymphocytes, and a mouse bone marrow micronucleus/sister chromatid exchange assay.

Urea was not genotoxic in several *in vitro* and *in vivo* assays. When tested at high concentrations some evidence of genotoxicity was demonstrated; however, urea is known to uncoil DNA and this property is likely linked to the genotoxic effects observed at high concentrations. Urea is not considered to have *in vivo* genotoxic activity at concentrations relevant to topical administration.

Reproductive Toxicity, Fertility

The effect on fertility of topically applied hydrocortisone or urea has not been evaluated in animals.

Developmental Toxicity

Subcutaneous administration of hydrocortisone to mice at doses of ≥30 mg/kg/day, to rabbits at a dose of 675 µg/kg/day, and the administration of a single intramuscular injection of ≥25 mg to hamsters during pregnancy produced fetal abnormalities including cleft palate.

While there are no clinical data available, the results of preclinical studies have demonstrated a lack of adverse effects on fetal development following topical application of a detergent containing up to 15 % urea to pregnant mice from Day 1-13 of gestation, and no effects on fetal development following oral administration with an aqueous solution of urea (2000 mg/kg) to rats and mice on days 10 and 12 of gestation.

REFERENCES

1. Almeyda J and Bur BW. Double blind controlled study of treatment of atopic eczema with a preparation of hydrocortisone in a new drug delivery system versus betamethasone 17-valerate. Br J Derm. 1974; 71:579
2. Almeyda J and Fry L. Controlled trial of the treatment of atopic eczema with urea. Hydrocortisone preparation versus betamethasone 17-valerate. Br J Derm. 1973; 88:493.
3. Ashton Ashton RE, Catterall M, Morley N, Fairris G, Joseph DN. A double-blind comparison of 0.25% and 0.05% desoxymethasone, 0.1% betamethasone valerate and 1% hydrocortisone creams in the treatment of eczema. J Int Med Res. 1987;15(3):160-6.
4. Ayers PJW and Hooper G. Assessment of the skin penetration properties of different carrier vehicles for topically applied cortisol. Br J Derm. 1978; 99:307.
5. British National Formulary for Children 2011-2012. Topical corticosteroids. BMJ Group, Pharmaceutical Press, RCPCH Publications Ltd. 2011; 13.4: 558-559.
6. Feldman RJ and Maiback HI. Percutaneous penetration of hydrocortisone with urea. Arch Derm. 1974; 109.
7. Floden CH, Hagerman G, Leczinsky CG, Skogh M, Swanbeck G. Calmurid as a base for the local treatment of eczema with steroids. Lakartigningen. 1971; 68:5160.
8. Gip L and Karltorp N. The rapidity of the effect of different types of topical corticosteroids. A double blind comparison between Diproderm ointment 0.05% and Calmurid-hydrocortisone 1%. Therapeutic Research. 1974; 16:300.
9. Greenish BV, Johnstone RS, Peel MJ. Simple hydrocortisone creams for dermatitis in general practice. Practitioner. 1986;230(1416):579-81.
10. Jacoby RJ and Gilkes JJH. A new urea hydrocortisone powder cream compared with other topical corticosteroid preparations: A six centre study. Curr med Res Opin. 1974; 2:474-481.
11. Khan SA. A double blind comparison of 1% hydrocortisone plus 10% urea (Alphaderm) and 0.05% fluocinonide (Metosyn) in the treatment of non-infective inflammatory dermatoses. Practitioner. 1978; 221:265.
12. Khan SA and Williamson DM. A double blind comparison of 1% hydrocortisone plus 10% urea (Alphaderm) and 0.1% betamethasone 17-valerate in the treatment of non-infective inflammatory dermatoses. Curr Med Res Opin. 1978; 5:354.
13. Laurberg G. Topical treatment with urea-hydrocortisone in atopic dermatitis: A controlled study against betamethasone 17-valerate. *Dermatologica*. 1975; 151:30.
14. McKenzie AW and Stroughton RB. Method of comparing percutaneous absorption of steroids. *Archives of Dermatology*. 1962; 86:608.
15. Pariser DM. Topical steroids: a guide for use in the elderly patient. Geriatrics. 1991;46(10):51-4, 57-60, 63.
16. Szarmach H, Weuta H, Stepka L. [Limitations of indications of clotrimazole-hydrocortisone and its components. A double-blind study]. Arzneimittelforschung. 1984;34(8):927-30.
17. Schmähl D. [Investigations on the influence of immunodepressive means on the chemical carcinogenesis in rats]. Z Krebsforsch Klin Onkol. 1974;81(3-4):211-5.
18. Wahberg JE and Swanbeck G. The effect of urea and lactic acid on the percutaneous absorption of hydrocortisone. *Acta Dermatovener Stockholm.* 1973; 53:207.

19. Whitefield M and McKenzie AW. A new formulation of 0.1% hydrocortisone cream vasoconstrictor activity and clinical effectiveness. *Br Jour Derm*. 1975; 92:585.
20. Allenby AC, Creasey NH, Edginton JAG, Fletcher JA, Shock C. Mechanism of action of accelerants of skin penetration. *Br Jour Derm*. 1969; 81(Suppl 4):47.
21. Barry BW and Woodford R. Proprietary hydrocortisone creams. Vasoconstrictor activities and bioavailability of 6 preparations. *Br Jour Derm*. 1976; 45:14.
22. Barry BW and Woodford R. Vasoconstrictor activities and bioavailabilities of seven proprietary corticosteroid creams assessed using a non-accluded multiple dosage regime; clinical implications. *Br Jour Derm*. 1977; 97:555.
23. Blank H, Hooper G, Kinmout PDC, Marks R, Stoughton RB, Williamson DM et al. Toical corticosteroid therapy, a round table discussion.
    Part I: Adverse effects of topical corticoids: Systemic. *Cutis*. 1979; 24:446.
    Part II: Adverse effects of topical corticoids: Local effects. *Cutis*. 1979; 24:633.
    Part III: Current concepts in hydrocortisone therapy. *Cutis*. 1980; 25:74.
    Part IV: The proper role of urea in managing skin disease. *Cutis*. 1980; 25:318.
24. Burdick KH, Poulsen B, Place VA. Extemporaneous formulation of corticosteroid for topical usage. *JAMA*. 1970; 211:462.
25. Das Gupta V. Effects of vehicle and other active ingredients on stability of hydrocortisone. *J Pharm Sc*. 1978; 67:229.
26. Gendrot D. Intérêts multiples de l'hydrocortisone locale. *Gaz Med France*. 1978; 85:826.
27. Goette DK and Odom RB. Adverse effects from topical steroids. *Cutis*. 1978; 21:624.
28. James MP, Black MM, Sparkes CG. Measurement of dermal atrophy reduced by topical steroids using a radio-graphic technique. *Br Jour Derm*. 1976; 95:14.
29. kaidbey KH, Kligman AM. Assay of topical corticosteroids. *Arch Dermatol*. 1976; 95:14.
30. Kligman AM and Kaidbey KH. Hydrocotrisone revisited: An historical and experimental evaluation. *Cutis*. 1978; 22:232.
31. Kligman AH. Dermatologic use of urea. *Acta Derm*. 1957; 37:155-159.
32. Miller JA, Munroe DD. Toipcal corticosteroids: Clinical pharmacology and therapeutic use. *Drugs*. 1980; 19:119.
33. Reddy BSN et al. A new model for human bio-assay of topical corticosteroids. *Brit Jour Derm*. 1976; 94:191.
34. Ritschel WA, Kitzmiller KW, Serraclion-Inglott A. Topical availability of hydrocortisone from different ointment bases. *Rev Can Biol*. 1973; 32:91.
35. Sarkany I, Hadgraft JN, Caron GA, Barrett CW. The role of vehicles in the percutaneous absorption of corticosteroids. *Brit Jour Derm*. 1965; 77:569.
36. Shahi V and Katz JL. Effect of formulation factors on penetration of hydrocortisone through mouse skin. *J Pharmaceut Sciences.* 1978; 7:789.
37. Stewart WD, Dantol JL, Maddin WS. Urea cream. *Cutis*. 1969; 5:1941.
38. Swanback G and Rajka G. Antipruritic effect of urea solutions. *Acta Derm Vener*. 1970; 50:225.
39. Wester RC, Noonan PK, Mailback HJ. Percutaneous absorption of hydrocortisone increases with long-term administration. *In vivo* study in the Rhesus monkey. *Arch Dermat*. 1980; 116:186.
40. Wilson L. The clinical assessment of topical corticosteroid activity. *Brit J Derm.* 1976; 94:33.
41. Hill CJ and Rostenberg A. Adverse effects from topical steroids. *Cutis*. 1978; 21:624

PART III: CONSUMER INFORMATION

Pr UREMOL® HC

**Hydrocortisone acetate USP 1% (w/w)
and Urea USP 10% (w/w) Cream**

**Hydrocortisone acetate USP 1% (w/v)
and Urea USP 10% (w/v) Lotion**

This leaflet is part III of a three-part 'Prescribing Information' and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about UREMOL® HC. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
UREMOL® HC is used to help relieve the dry skin, redness, and itchiness of certain skin problems for up to 4 weeks.

What it does:
UREMOL® HC contains hydrocortisone which belongs to a group of medicines called steroids. Steroids help to reduce redness, swelling and irritation of the skin. UREMOL® HC also contains urea, a type of medicine known as an emollient. Emollients work by hydrating the skin and also by helping your skin absorb steroids.

When it should not be used:
Do not use UREMOL® HC if you:

- are allergic to hydrocortisone, other corticosteroids, urea, any component of the container, or to any of the other ingredients in UREMOL® HC (see **What the nonmedicinal ingredients are**).
- have bacterial, tubercular, fungal, parasitic, viral skin infections (e.g. herpes simplex, chicken pox, vaccinia), tuberculosis or syphilis skin lesions, or a skin reaction following a recent vaccination.
- have acne, rosacea (a facial skin condition where the nose, cheeks, chin, forehead or entire face are unusually red, with or without tiny visible blood vessels, bumps (papules) or pus-filled bumps (pustules)), or itchy skin which is not inflamed.

Do not apply in or near the eye.

If you think any of these apply to you, don't use UREMOL® HC until you have checked with your doctor or pharmacist.

What the medicinal ingredient is:
Hydrocortisone acetate and urea

What the nonmedicinal ingredients are:
The nonmedicinal ingredients in UREMOL® HC Cream are propylene glycol, capric/caprylic triglyceride, isopropyl myristate, xanthan gum, sodium lauryl sulfate, edetate disodium, Ceteareth-12, Ceteareth-20, glyceryl stearate, octyldodecanol, potassium phosphate monobasic, sodium phosphate dibasic, cetyl alcohol, lanolin alcohol/mineral oil, purified water; and Germaben II (parabens) as preservative.

The nonmedicinal ingredients in UREMOL® HC Lotion are disodium edentate, sodium phosphate dibasic anyhydrous, citric acid anhydrous, xanthan gum, glycerin, Ceteareth-12, Ceteareth-20, glyceryl stearate, capric/caprylic triglyceride, octyldodecanol, acetylated lanolin alcohol/cetyl stearate, isopropyl myristate, purified water; and Germaben II (parbens) as preservative.

What dosage forms it comes in:
UREMOL® HC Cream is available in a 50 g tube and 225 g jar.

UREMOL® HC Lotion is available in a 150 mL tube.

WARNINGS AND PRECAUTIONS

Topical corticosteroids when used over large areas, on sensitive areas such as the face, in skin-fold areas like the armpit and groin, on broken skin, for prolonged periods or under an airtight dressing are more likely to be absorbed into the bloodstream and cause side effects. Apply only enough to cover the affected areas. UREMOL® HC should not be applied over large areas unless advised by a physician.

Only use UREMOL® HC for as long as your doctor recommends.

Inform your doctor if you have previously used corticosteroids.

Before using UREMOL® HC, talk to your doctor or pharmacist if:

- you are pregnant or planning to become pregnant.
- you are breastfeeding. If you do use UREMOL® HC when breastfeeding, do not use on your breast area to ensure that the baby does not accidentally get it in their mouth.
- you have other inflammatory skin diseases in the leg as a result of impaired circulation (such as stasis dermatitis).
- you have problems with your kidney or liver. You may need to use a smaller amount of UREMOL® HC or use it less often.

While using UREMOL® HC, talk to your doctor or pharmacist if:

- you develop any skin infection
- you have an allergic reaction
- you develop significant skin irritation or stinging
- you experience skin thinning or softening
- your condition worsens or does not improve

While using UREMOL® HC:

- UREMOL® HC may cause local skin reactions (e.g. dermatitis).
- In the case of skin irritation, discontinue use temporarily. UREMOL® HC may sting when applied to damaged skin.
- UREMOL® HC should be used with caution on the face, or in skin fold areas, such as the groin or the armpit.
- Avoid UREMOL® HC from getting in the eye, or other mucous membranes. In case of contact, wash with water. Absorption in the body may cause increased pressure in the eye (glaucoma), or a cloudy lens in the eye (cataracts).
- Do not use occlusive dressings such as a bandage, nor cover the treated areas tightly.
- If you are over 65 years of age, use UREMOL® HC caution. You may need to use a smaller amount of UREMOL® HC or use it less often.
- Children absorb larger amounts of topical corticosteroids and therefore, may be more likely to develop side effects. **UREMOL® HC is not recommended for use in children under 2 years of age**.
- If you have any skin disease around a leg ulcer, use of a topical corticosteroid may increase the risk of an allergic reaction or an infection around the ulcer.
- UREMOL ® HC is for external use only. Avoid use on open wounds.

INTERACTIONS WITH THIS MEDICATION

Some medicines may affect how UREMOL® HC works, or make it more likely that you'll have side effects. Examples of these medicines include:

- Ritonavir (for HIV).
- Itraconazole (for fungal infections).

UREMOL® HC may increase the amount that other medications are absorbed through the skin.

Tell your doctor or pharmacist about all your other medications, including medicines that you bought without prescription and natural health products.

PROPER USE OF THIS MEDICATION

For topical use only and not for use in the eyes.

Use in children should be under the supervision of an adult.

Do not use in children under 2 years of age, unless directed by a doctor or pharmacist.

Usual dose:
Apply a thin film to the affected areas once or twice a day for a maximum of 4 weeks.

It is important to not stop using UREMOL® HC suddenly or your skin condition could flare up again. If your condition does not improve within 2-4 weeks of treatment, speak to your doctor or pharmacist.

If you use UREMOL® HC regularly make sure you talk to your doctor before you stop using it.

How to Apply UREMOL® HC:

- The affected area should be clean and dry.
- Apply a thin layer and gently rub in, using only enough to cover the entire affected area.
- Wash your hands after use unless treating the hands.
- Excess product should not be returned to the container, since it may cause contamination.
- A moisturizer should be used as maintenance therapy.

UREMOL® HC should be used for the minimum amount of time required to achieve the desired results, **but always use UREMOL® HC exactly as your doctor has told you**. Check with your doctor or pharmacist if you are not sure.

Overdose:
Excessive topical application of UREMOL® HC may result in severe skin irritation.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use UREMOL® HC, apply it as soon as you remember. If it is close to the time scheduled to apply your next dose, wait and apply your next scheduled dose and then continue as before. Do not apply extra UREMOL® HC to make up for missed doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines UREMOL® HC can have side effects although not everybody gets them. Side effects will affect your skin and may have an effect on other parts of your body if a sufficient quantity of medicine is absorbed through the skin and enters your blood stream.

If your skin condition gets worse or your skin becomes swollen during treatment. You may be allergic to the medicine or need other treatment. Stop using UREMOL® HC and tell your doctor as soon as possible.

The following side effects have been reported in patients using UREMOL® HC and other corticosteroids:

- local hypersensitivity
- contact dermatitis/dermatitis (a type of eczema)
- redness
- rash
- hives
- itching
- skin burning
- skin pain
- skin dryness or flaking
- skin thinning or softening
- stretch marks
- changes in the colour of your skin
- increased body hair
- the appearance of blood vessels under the surface of your skin (telangiectasia)
- worsening of condition
- secondary infection
- application site irritation or pain

The following have been observed with the use of airtight dressings:

- pus-filled bumps (pustules), heat rash (miliaria), inflammation of the hair follicles (folliculitis), non-healing wounds (pyoderma)

Serious side effects such as Cushing's syndrome may be associated with absorption in the body of topical corticosteroids (for example, from long-term, improper or excessive use). Symptoms include: increased weight, moon face / rounding of the face and obesity. Other side effects may include weight loss, fatigue, nausea, diarrhea and abdominal pain (steroid withdrawal syndrome). Also, look out for delayed weight gain and slow growth in children.

Other symptoms that may only show in blood tests or when your doctor gives you a medical examination are: decreased hormone cortisol levels in your blood, increased sugar levels in your blood or urine, high blood pressure, cloudy lens in the eye (cataract), increased pressure in the eye (glaucoma), as well as weakening of the bones through gradual mineral loss (osteoporosis) and additional tests may be needed after your medical examination to confirm whether you have osteoporosis.

If any of the side effects listed becomes severe or troublesome, tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Allergic reactions: rash, hives, swelling of the skin.			✓
Cushing's syndrome: weight gain, moon face / rounding of the face and obesity.			✓

This is not a complete list of side effects. For any unexpected effects while taking UREMOL® HC *contact your doctor or pharmacist.*

HOW TO STORE IT

Store between 15° and 30°C. Keep out of direct sunlight.
Keep out of the sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.stiefel.ca or by contacting the sponsor,

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This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: February 18, 2014