PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ERFA HYDROQUINONE

Hydroquinone
Gel, 4% w/w for topical use

FOR EXTERNAL USE ONLY
Anti-hyperpigmentation agent

ERFA
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ERFA HYDROQUINONE is indicated for: the short-term treatment of hyperpigmented skin conditions such as chloasma, melasma, 'liver spots', 'age spots', freckles, senile/solar lentigines, and post-inflammatory hyperpigmentation.

- UV protection (sunscreen, and/ or protective clothing) should be used. See **Warnings and Precautions**.

- If reduction of pigmentation is not observed within 8-12 weeks of treatment (3 weeks for melasma), therapy should be discontinued and the hyperpigmented skin assessed for potentially more serious conditions. See **Warnings and Precautions.**

- Hyperpigmented skin should be thoroughly assessed for malignant lesions.

1.1 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years): No appropriate data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

ERFA HYDROQUINONE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **Dosage Forms, Strengths, Composition and Packaging**.
The safety of topical hydroquinone use during pregnancy or for children has not been studied.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

Test for skin sensitivity before use:
Apply a small amount of gel on unbroken skin, and check for irritations within 24 hours. Minor redness is not necessarily a contraindication, but treatment should be discontinued if itching, excessive inflammation, or vesicle formation occurs.

Dosing:
ERFA HYDROQUINONE should be applied to affected areas and rubbed in well twice daily, in the morning and before bedtime, or as directed by a physician. If no improvement is seen after 2 months of treatment (within 3 weeks for melasma), ERFA HYDROQUINONE should be discontinued, and the skin reassessed for potentially more serious conditions.

Hydroquinone gel should not be used for maintenance therapy beyond 2 or 3 months. UV protection

(sunscreen SPF > 30 (UVA and UVB), and/ or protective clothing) should be used. See **Warnings and Precautions**.

The use of hydroquinone products in paranasal and infraorbital areas increases the risk of irritation. Discontinue use if mild irritation persists or if severe irritation or rash occurs.

Health Canada has not authorized an indication for pediatric use. (See **1.1 Pediatrics)**

3.2 Administration

For topical use only. Not for oral, ophthalmic or intravaginal use.

4 OVERDOSAGE

Consumption of large acute doses of hydroquinone-containing mixtures, accidentally or with suicidal intent (≥ 1 g of hydroquinone), has been reported to produce signs of acute CNS disturbances such as tremor, dizziness, muscular twitching, headache, and delirium, in addition to tinnitus, nausea, respiratory difficulty, convulsions, and unconsciousness. If overdoses of hydroquinone are ingested, treat symptomatically.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

ERFA HYDROQUINONE is a clear, transparent gel with a characteristic odour. Each gram of ERFA HYDROQUINONE gel contains 40 mg of hydroquinone. **The packaging unit (tube) contains 30 g of hydroquinone gel 4%.** Excipients: Ethanol 96%, glycolic acid, propylene glycol, polyquaternium-10, ammonium hydroxide, citric acid anhydrous , sodium metabisulfite , sodium sulfite anhydrous , disodium edetate, butylhydroxytoluene and purified water.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Hydroquinone gel 4% w/w	Ammonium hydroxide, butylhydroxytoluene , citric acid anhydrous, disodium edetate, ethanol 96%, glycolic acid, propylene glycol, polyquaternium-10, sodium metabisulfite , sodium sulfite anhydrous, and purified water.

6 WARNINGS AND PRECAUTIONS

Hydroquinone may produce exogenous ochronosis with continuous use (progressive asymptomatic hyperpigmentation of gray-blue or blue-black darkening of the skin, erythema, and papules on the sun exposed treated areas of the skin). In severe cases, ochronosis may cause disfiguring effects. If hyperpigmentation develops, treatment should immediately be discontinued. To reduce risk of exogenous ochronosis, hydroquinone should not be used with concomitant photosensitizing drugs (e.g. antimalarial drugs, resorcinol, phenol or injections of quinine).

Hydroquinone may produce leukoderma if used for a relatively long period of time. Leukoderma is mostly irreversible as melanocytes are destroyed leaving white patches on the skin. It may possibly mask

other skin lesions, including malignant lesions.

General

Hydroquinone is a skin-bleaching agent, which may produce unwanted cosmetic effects. Use only as directed. The physician should be familiar with conditions of use of hydroquinone for skin application before prescribing. The skin lesions should be assessed by the physician before prescribing the drug in order to exclude malignant skin lesions.

UV protection (sunscreen, and/or protective clothing) should be used to avoid re-pigmentation. Hyperpigmentation or depigmentation during treatment should prompt discontinuation of therapy. Hydroquinone should only be applied to small areas of the body, and should not be applied on broken skin or mucous membranes. Avoid contact with eyes; in case of contact, the patient must rinse thoroughly with water.

If no improvement is seen after 2 or 3 months of treatment (within 3 weeks for melasma), ERFA HYDROQUINONE should be discontinued, and the skin reassessed for potentially more serious conditions.

ERFA HYDROQUINONE contains glycolic acid and citric acid, which are alpha-hydroxy acids (AHAs) which may increase the skin's sensitivity to the sun and particularly the possibility of sunburn. It is recommended that prior to exposure to the sun, users cover areas where AHAs have been applied with sunscreen. Contact of the product with the skin must be of limited frequency or duration. See **Warnings and Precautions – Immune**.

ERFA HYDROQUINONE contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or asthmatic episodes. Sulfite sensitivity is more frequently reported among asthmatic subjects.

This medicinal product can cause local skin reactions (such as contact dermatitis) or irritation of the eyes and mucous membranes as it contains butylhydroxytoluene. See **Warnings and Precautions – Immune**.

Carcinogenesis and Mutagenesis
Long term exposure to hydroquinone in animal carcinogenicity studies has shown some evidence of carcinogenicity. Published studies have demonstrated that hydroquinone is a mutagen and a clastogen. See **NON-CLINICAL TOXICOLOGY**.

Dermal application of hydroquinone was associated with cutaneous malignancy (spindle cell squamous cell carcinoma) in some cases reported in the literature. It is unknown whether hydroquinone was a pro-carcinogen or malignancy was due to suppression of natural photo-protection effect of melanin.

Caution should be exercised in patients who have a history of, or are at risk of developing cancer when using hydroquinone-containing products. Close monitoring should be considered.

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

Allergic contact dermatitis may occur. If contact dermatitis is reported or suspected, ERFA HYDROQUINONE should be discontinued immediately. (See **ADVERSE REACTIONS - Adverse Reaction Overview**.)

Sexual Health

Reproduction and Fertility
Oral administration of hydroquinone did not produce embryotoxic, fetotoxic, or teratogenic effects in rats, nor did it produce significant adverse reproductive effects in a two-generation study. However in rabbits, various teratogenic/reproductive treatment-related effects were observed at high doses. (See **NON-CLINICAL TOXICOLOGY**). Animal reproduction studies have not been conducted with topical hydroquinone. It is also not known whether topical hydroquinone can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Topical hydroquinone should be given to a pregnant woman only if clearly needed.

Skin
This product contains glycolic acid and citric acid, which are alpha-hydroxy acids (AHAs) which may increase the skin's sensitivity to the sun and particularly the possibility of sunburn. It is recommended that prior to exposure to the sun, users cover areas where AHAs have been applied with sunscreen.
Contact of the product with the skin must be of limited frequency or duration.
This medicinal product can cause skin irritation as it contains propylene glycol.
This medicinal product can cause local skin reactions (such as contact dermatitis) or irritation of the eyes and mucous membranes as it contains butylhydroxytoluene.

6.1 Special Populations

6.1.1 Pregnant Women

The safety of topical hydroquinone use during pregnancy has not been studied. Topical hydroquinone should be given to a pregnant woman only if the treatment benefit outweighs the perceived risks.

6.1.2 Breast-feeding

The safety of topical hydroquinone use during breast-feeding has not been studied. It is unknown if the drug is excreted in human milk. However, because many drugs are excreted in human milk, ERFA HYDROQUINONE should not be used during breast-feeding.

6.1.3 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

ERFA HYDROQUINONE has not been adequately studied in elderly patients Health Canada has not authorized an indication for geriatric use.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

In published clinical trials of varying duration (most were of 12-week duration), the adverse effects

reported in 559 patients treated with various formulations of hydroquinone cream (2% or 4%) mainly for melasma were local irritation, erythema, itchy eruptions, stinging, tingling, burning, pruritus at the application site. Most events were mild in intensity. Contact dermatitis was reported in three patients, one patient had a positive patch test for sensitization.

Spontaneous adverse event reports in Canada for hydroquinone topical skin products include the following events: contact dermatitis, burning sensation, skin discolouration/ hyperpigmentation, rash, serious rash, chemical burn, scarring, drug ineffective, serious erythema, and benign neoplasm of the skin.

Long term treatment with hydroquinone may result in ochronosis or leukoderma (see **Warnings and Precautions**).

Sulfite Sensitivity Reactions: Sulfite may cause allergic-type reactions (including anaphylaxis and life-threatening reactions and asthmatic episodes) in certain susceptible individuals. See **Warnings and Precautions**.
This product contains glycolic acid and citric acid, which are alpha-hydroxy acids (AHAs) which may increase the skin's sensitivity to the sun and particularly the possibility of sunburn.
This product can cause skin irritation as it contains propylene glycol.
This product can cause local skin reactions (such as contact dermatitis) or irritation of the eyes and mucous membranes as it contains butylhydroxytoluene.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.
In a study to demonstrate the efficacy and safety of a novel pharmaceutical formulation of hydroquinone 4%, in the gel form (HQ*-4% (02-0268)) there were no severe adverse reactions detected.
In the study, 48.3% of participants experienced adverse reactions out of which 43.3% were related to the product. There was only one adverse reaction which caused withdrawal in the control group (desquamation), 51.7% of the patients from the control group experienced no adverse reactions, 35 % experienced one adverse reaction, 6.7 % experienced two adverse reactions, 5.0% experienced three adverse reactions., and 1.7% experienced 4 adverse reactions.

Table 1 Summary of related AE by organ system and preferential terminology (MedDRA dictionary) from the clinical assay HQ*-4% (02-0268)

	Hydroquinone gel 4% n (%)	**placebo n = (%)**
Eye disorders	**1 (3.57)**	-
Eye irritation	1 (3.57)	-
General disorders and administration site	**13 (46.43)**	**10 (31.25)**
Application site desquamation	1 (3.57)	-
Application site dryness	2 (7.14)	-
Application site erythema	2 (7.14)	-
Application site pruritus	9 (32.14)	10 (31.25)
Respiratory, thoracic and mediastinal disorders	-	**2 (6.25)**
Nasal passage irritation	-	1 (3.13)
Sneezing	-	1 (3.13)
Skin and subcutaneous tissue disorders	**4(14.29)**	**2 (6.25)**

Dermatitis acneiform	3 (10.71)	-
Dermatitis exfoliative	1(3.57)	1(3.13)
Face oedema	-	1(3.13)

The most frequent adverse reactions reported in the clinical study were application site disorders with 46.43% of patients in the control group and 31.25% of patients in the placebo group. Skin and subcutaneous tissue disorders were the second most frequently reported adverse reaction with 14.29% of patients in the control group and 6.25% of patients in the placebo group. Two cases of respiratory, thoracic and mediastinal disorders were reported in the placebo group (nasal passage irritation and sneezing) resulting with 6.25% of the placebo group participants. Only one case of eye disorder (eye irritation) was reported in the study (3.57%)

7.3 Clinical Trial Adverse Reactions (Pediatrics)

ERFA HYDROQUINONE was not studied in pediatric populations.

7.4 Post-Market Adverse Reactions

The frequency is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1.000), very rare (<1/10,000) and unknown frequency (cannot be estimated from the data available).

Skin and subcutaneous tissue disorders
Uncommon: erythema and itching.
Rare: cutaneous sensitivity. In long-term treatment it can cause a cutaneous hyperpigmentation reaction.

The treatment should be discontinued if these disorders do not disappear after one week.

Very rare: leukoderma has been observed in isolated cases. Ochronosis has been observed in long-term treatments (more than 6 months), mainly in black people.

No systemic adverse effects have been described.

TREATMENT SHOULD BE STOPPED IF ADVERSE REACTIONS ARE OBSERVED.

8 DRUG INTERACTIONS

8.1 Overview

Peroxides: hydroquinone should not be used simultaneously with peroxides (for example: oxygenated water, benzoyl peroxide, etc.). (See **Drug-Drug interactions**).
Photosensitizing drugs: hydroquinone should not be used with concomitant photosensitizing drugs. (See **Drug-Drug interactions**).

8.2 Drug-Drug Interactions

The simultaneous use of *hydroquinone* with peroxides (for example: oxygenated water, benzoyl peroxide, etc.) can cause temporary coloration of the skin, due to the oxidation of *hydroquinone.* This temporary coloration is eradicated by stopping the use of one of these medicinal products and washing the area of application with mild soap.

Photosensitizing drugs:
To reduce risk of exogenous ochronosis, hydroquinone should not be used with concomitant photosensitizing drugs (e.g., antimalarial drugs, resorcinol, phenol or injections of quinine). Many other commonly used medications may have photosensitizing properties to some degree.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Topical application of hydroquinone produces a reversible depigmentation of the skin by inhibition of the enzymatic oxidation of tyrosine to 3, 4-dihydroxyphenylalanine (dopa) which is involved in the initial step of the melanin pigment biosynthesis pathway and suppression of other melanocyte metabolic processes. Exposure to sunlight or ultraviolet light will cause repigmentation of bleached areas.

9.2 Pharmacodynamics

Accumulation of melanin in the upper layer of the epidermis is the main cause for pigmentation disorders. Melanin is a durable polymer, and there is almost no available means of destroying its structure and lightening the skin. Thus, inhibition of synthesis of melanin is the approach most often used for reducing melanin content in the epidermis. Hydroquinone affects melanogenesis by competing with tyrosine for the enzyme tyrosinase for oxidation; in the presence of catalytic amounts of dopa, hydroquinone is oxidized to the toxic benzoquinone metabolite which could damage membranes; hydroquinone inhibits DNA and RNA synthesis and alters melanosome formation; histochemical and electron microscopy indicated that hydroquinone affects the membranous structures of melanocytes and eventually causes necrosis of whole melanocytes.

9.3 Pharmacokinetics

Absorption:

Absorption of orally administered or intratracheally instilled hydroquinone is rapid and extensive (Garton & Williams, 1949; Divincenzo et al., 1984; English et al., 1988). However, the rate of hydroquinone absorption through the skin is low. Marty et al. (1981) reported that the in vitro permeability constants for rat and human skin were 28×10^{-6} and 4×10^{-6} cm/hr, respectively. Based on the data of Bucks et al. (1988), an in vivo human dermal absorption rate of 3 $\mu g/cm^2$/hr and a permeability constant of 2.25×10^{-6} cm/hr can be calculated. The actual amount of hydroquinone absorbed following dermal exposure depends on the exposure concentrations, length of exposure and vehicle, as well as other factors. When Bucks et al. (1988) applied ^{14}C-labelled hydroquinone in an alcoholic vehicle to the foreheads of human volunteers for 24 hours, 57% of the total ^{14}C label was excreted in the urine after 5 days. Addition of a sun screen to the hydroquinone solution reduced total excretion to 26%.

Distribution:

Following the oral administration of radiolabelled hydroquinone to F-344 rats, radioactivity was widely distributed throughout the animal tissues. The highest activity was localized in the kidney and liver (Divincenzo et al., 1984). However, on a quantitative basis, the amount retained within the animal was low, representing < 2% of the total dose 48 hours after exposure (Divincenzo et al., 1984; English et al., 1988). Widespread distribution and extensive elimination were also observed following intratracheal administration of hydroquinone to F-344 rats (Lockhart & Fox, 1985b). However, following the intravenous injection of radiolabelled hydroquinone to F-344 rats, radioactivity was shown, using whole

body autoradiographic techniques, to concentrate in the bone marrow, thymus and white pulp of the spleen (Greenlee et al., 1981a). Subsequent experiments indicated that significant acid soluble and covalently bound radioactivity could be recovered in the thymus, bone marrow and white blood cells 24 hours after intravenous administration (Greenlee et al., 1981b). These results indicate that the route of administration may influence the profile of distribution and elimination observed following hydroquinone administration.

Metabolism:

Hydroquinone is converted mainly by Phase II metabolism to water-soluble conjugates, as shown by the recovery of only little parent compound and p-benzoquinone (0.25-7%) but large amounts of hydroquinone-monoglucuronide and hydroquinone-monosulfate (>90%) in the urine (Divincenzo et al. 1984; English et al. 1988). A small percentage of the dose was recovered as the mercapturic acid conjugate of hydroquinone, suggesting the intermediate formation of a glutathione conjugate of hydroquinone.

Divincenzo et al. (1984) demonstrated that repeated dosing with 200 mg hydroquinone/kg did not alter the relative or absolute rat liver weight or induce the hepatic mixed-function oxidase system, nor did hydroquinone undergo Phase I oxidation to other metabolites such as 1,2,4-trihydroxybenzene. In addition, the formation of 1, 2, 4-trihydroxybenzene was not observed in the urine after oral administration of hydroquinone to rabbits (Garton & Williams, 1949). However, following intraperitoneal injection of hydroquinone (50 mg/kg) in Wistar rats and Japanese white rabbits, 1, 2, 4-trihydroxybenzene represented a significant proportion (approximately 12%) of the metabolites recovered in the urine (Inoue et al., 1989a, b). This apparent difference in the metabolic profile observed when hydroquinone is administered by the intraperitoneal route rather than the oral route is probably related to the ability of the gastrointestinal system to conjugate phenolic compounds absorbed in the intestine, thus reducing the amount of free hydroquinone available for Phase I metabolism in the liver (Powell et al., 1974; Cassidy & Houston, 1980a, b; Cassidy & Houston, 1984).

Elimination:

Hydroquinone is excreted mainly in the form of water-soluble metabolites via the urine (about 90%). Dose-related differences have been observed for rats receiving 25 or 350 mg/kg, which suggests that elimination processes are saturated at high-dose levels (English et al., 1988). The area under the curve (AUC) values for plasma concentration, which provide an index of bioavailability, also showed that saturation of elimination had occurred at high-dose levels, particularly for females. The fact that most of the radioactivity excreted is associated with the alpha-elimination phase suggests that this may be due to conjugation of hydroquinone to readily excreted metabolites. The appearance of a double peak in the blood concentration versus time curve indicates that enterohepatic recycling of hydroquinone may have occurred.

Permeation study (UIBF 03.09.60 (V)):

Transdermal permeability of hydroquinone in two semisolid (gel) formulations and a semisolid reference formulation using FRANZ type diffusion cells was studied. The capacity of hydroquinone to permeate the skin was established by determining the quantities of the agent that had crossed it at each of the prefixed time interval. No significant differences were seen between the three formulations in terms of the permeation variables studied (transdermal flow rate, latency and quantity permeated per unit time) ($p=>0.1$).

10 STORAGE, STABILITY AND DISPOSAL

Store at room temperature between 15 -30 ^{o} C. Do not freeze. Keep the tube totally sealed to protect it from light. Keep out of the sight and reach of children. Do not use the product if dark coloration is observed, even if it is within the expiry period.

11 SPECIAL HANDLING INSTRUCTIONS

Wash hands with soap after the application of the product, as *hydroquinone* can cause reversible brown spots on the fingernails.

PART II: SCIENTIFIC INFORMATION

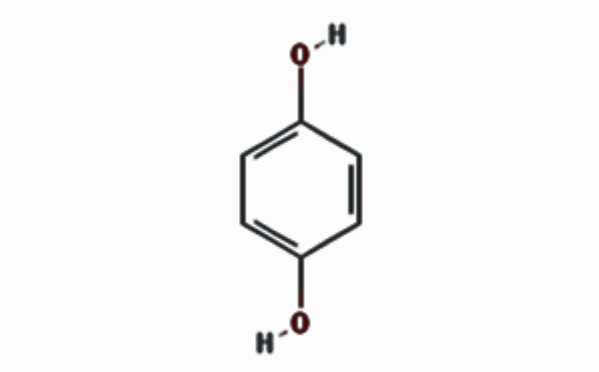
12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Hydroquinone

Chemical name: Benzene-1,4-diol
Molecular formula and molecular mass: $C_6H_4(OH)_2$, Mass: 110.112 g/mol

Structural formula:



Physicochemical properties: **Hydroquinone**, also **benzene-1,4-diol** or **quinol**, is an aromatic organic compound that is a type of phenol, a derivative of benzene. Hydroquinone is a white granular solid at room temperature and pressure.

13 CLINICAL TRIALS

Hydroquinone has been considered the gold standard for treatment of hyperpigmentation for more than 50 years. Therefore, the clinical studies reported in literature compared new depigmentation products to hydroquinone cream. Two studies in melasma patients compared 4% hydroquinone cream with placebo. Overall, the studies enrolled few patients and had a large degree of variation in design, which precluded the combination of efficacy data for statistical analysis. Studies investigated efficacy and safety of hydroquinone in the treatment of lentigines (one study), melasma (most studies), and combination of hyperpigmentary conditions (four studies).

Assessment of efficacy varied among studies, subjective assessments employing variable scales and objective assessments using instruments to measure reflective light at the pigmented area. Not all studies applied both subjective and objective efficacy criteria and one did not report the scale used for assessing clinical improvement.

In a randomized, double blind, placebo-controlled study, hydroquinone 4% cream b.i.d. with sunscreen was compared to placebo plus sunscreen (Ennes et al. 2000). All subjects had a clinical diagnosis of melasma on the face and were from 19 to 55 years of age. The study was performed during the period from autumn to spring in Brazil (however, there are sunny days throughout the whole year). Complete disappearance of the melasma was reported in 8/21 (38%) patients in the hydroquinone group at 12 weeks of treatment compared to 2/24 (8%) patients in the placebo group and therapeutic failures occurred in 4/24 (17%) patients in the placebo group. Clinical improvements were observed within 3 weeks of treatment. The importance of concomitant use of sunscreen of at least SPF 30 to prevent re-pigmentation

was emphasized when treating melasma patients with hydroquinone. The Lima Haddad et al. study used the split design in which one group of patients with melasma (n=12) received on each half of the face, either hydroquinone 4% or placebo once a day. Clinical improvement of melasma was reported in the hydroquinone and a test formulation groups in 77% and 67% of patients, respectively (no significant differences).

The study of Chan et al., (2008) was the only one that performed a subgroup analysis on the skin phototype and type of melasma. It was a multicenter, randomized, parallel controlled, investigator blinded sudy in which East and South-East Asian patients aged 29-70 years, with a clinical diagnosis of moderate to severe melasma, were enrolled. Patients were treated daily for 8 weeks with a triple therapy (TT) cream (one application at bedtime) or hydroquinone 4% cream (twice daily). The primary efficacy variable was melasma global severity score (GSS: 0, none [melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation]; 2, moderate [moderately darker than the surrounding normal skin]; and 3, severe [markedly darker than the surrounding normal skin]. Results showed that 95% patients completed the study; in the TT group 77/120 (64%) patients had a GSS of 'none' or "mild' at week 8 compared to 48/122 (39%) patients on hydroquinone ($p<0.001$). Efficacy subgroup analysis revealed that hydroquinone effects were superior in skin phototype III as compared to skin phototype IV and more effective in reducing pigmentation in epidermal melasma as compared to mixed or dermal melasma.

In all these studies, efficacy of hydroquinone was assessed from the changes from baseline, but without the inclusion of placebo groups, therefore, it is difficult to ascertain whether any change can be attributed to the drug under consideration.

Most of the studies showed that application of hydroquinone 2% to 4% had a reduction in pigmentation intensity at the end of treatment. Either brand name or generic formulations were used. Most studies had a treatment period of 8 to 12 weeks.

13.1 Trial Design and Study Demographics

Table 2 - Summary of patient demographics for clinical trials in demonstration of the efficacy of externally used hydroquinone 4% gel in depigmentation of melasma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
HQ*-4% (02-0268)	Phase III study, parallel, comparative, double-blind, placebo-controlled, randomized, prospective and multicentric.	Application of a thin gel layer over hyperpigmented areas. Single daily application at the beginning of the night for 90 days.	60	38.77 ± 7.9 (18-65)	1 male 59 females

Patients involved in the study had a mean age of 38.77 ± 7.9 years, with similar distribution of this parameter in both arms of the study. Female patients (98.3%) constituted the largest group by sex since there was only one male patient included in the placebo group.

13.2 Study Results

Table 3 - Results of the study in demonstration of the efficacy of externally used hydroquinone 4% gel in depigmentation of melasma

Primary Endpoint	Associated value and statistical significance for drug at specific dosages	Associated value and statistical significance for placebo or active control
Percentual decrease of the pigmentation intensity after 12 weeks	53.27% (p=0.0056)	33.59%

14 NON-CLINICAL TOXICOLOGY

Dermal toxicity:

Dermal application of hydroquinone to rats and mice at doses of up to 3840 mg/kg and 4800 mg/kg, respectively for 14 days did not result in local or systemic adverse effects (NTP 1989). A dermal cancer bioassay was conducted by applying hydroquinone to the skin of ICR/HA Swiss mice, 3 times a week for one year (Va Duuren &Golschmidt, 1976). The hydroquinone-exposed mice did not develop any skin tumors at the site of application, and the number of skin tumors in mice treated with benzo[a]pyrene and hydroquinone was lower than in mice treated with B[a] P alone. In a second smaller study with Sutter mice, a solution of 20% hydroquinone in acetone applied twice a week for 12 weeks to the dorsal skin of mice did not promote the development of tumor in skin that had been initiated with dimethylbenzanthracene (O'Donogue 2006).

Hydroquinone was applied to both epilated and unepilated skin of eight black guinea-pigs at concentrations of 1, 3, 5, 7 and 10% in three vanishing creams (Bleehen et al., 1968). The number of animals per dose group was not reported. Six animals served as controls. The material was applied once daily, five times a week, for one month. Hydroquinone was irritating only at concentrations of 5% or more. Weak to moderate depigmentation occurred in all areas of skin to which creams containing 1-10% hydroquinone were applied.

Dermal application of 25 or 150 mg/kg hydroquinone to rats produced slight to severe erythema.

In a Magnusson-Kligman guinea pig maximization test, hydroquinone was classified as an extreme sensitizer. Hydroquinone was positive for sensitization in an LLNA.

The dermal LD50 value has been estimated to be > 3800 mg/kg in rodents.

Hydroquinone (2% in a topical cream) caused liver and kidney damage when administered to rabbits (n=6) for 6 weeks. The test substance was administered daily to 1 or both ears (volume not specified) of the rabbits or to the shaved abdomen (2 g/cm^2); the rabbits were killed and necropsied. Findings in the liver included hydropic degeneration, bile duct hyperplasia, and glycogen depletion. Hydropic degeneration, hyaline casts, congestion, perivascular edema, and fibrosis were observed in the kidneys. For both the kidneys and livers, the effects were greater in the groups in which the test substance was administered to the ears. Dermal effects included hyperkeratosis, lymphocytic and eosinophilic infiltration, and congestion of dermal blood vessels. Dermal depigmentation was observed when hydroquinone (5% in 25 µL propylene glycol/ethanol, 50:50) was dermally administered to multiple sites of the backs of Yucatan miniature pigs (n=2) twice/day, 7 days/week for 90 days. Microscopic examination of biopsies from the test area showed decreased pigment and melanocytes.

Oral toxicity:

Oral LD50 values for several animal species range between 300 and 1300 mg/kg body weight. However, for the cat LD50 values range from 42 to 86 mg/kg body weight. Acute high-level exposure to hydroquinone causes severe effects on the central nervous system (CNS) including hyperexcitability, tremor, convulsions, coma and death. At sub-lethal doses these effects are reversible. The dermal LD50 value has been estimated to be > 3800 mg/kg in rodents.

A 6-week oral toxicity study in male F-344 rats resulted in nephropathy and renal cell proliferation. Thirteen-week oral gavage studies in F-344 rats and in B6C3F1 mice resulted in nephrotoxicity in rats at 100 and 200 mg/kg, and tremors and convulsions in rats at 200 mg/kg; reduced body weight gain was seen in both rats and mice. Dosing at 400 mg/kg was lethal in rats. In mice dosed for 13 weeks at 400 mg/kg, tremors, convulsions and lesions in the gastric epithelium were reported. Thirteen-week hydroquinone exposure of Sprague Dawley rats resulted in decreased body weight gain and CNS signs at 200 mg/kg. CNS signs were also observed at a dose level of 64 mg/kg body weight but not at 20 mg/kg.

Administration of hydroquinone to rats in drinking water (2,500 - 10,000 ppm) for 8 weeks resulted in significant increases in liver and kidney weights. Hydroquinone administered orally to rats (63 - l000 mg/kg) and mice (31 - 500 mg/kg) for 14 days resulted in tremors and deaths in the high-dose groups. Dermal administration to rats (240-3840 mg/kg) and mice (300 - 4800 mg/kg) for 14 days caused neither death nor any significant adverse effects. For mice given i.p. injections of 10 mg/kg hydroquinone for 6 weeks, it was concluded that hydroquinone may cause hematologic injury.

Rats given 1000 - 4000 ppm hydroquinone in drinking water for 15 weeks had significantly increased liver and kidney weights. Oral administration of 25–400 mg/kg hydroquinone to rats and mice for 13 weeks resulted in mortality in the high-dose groups for both rats and mice. Other adverse signs, such as lethargy, tremors, and changes in relative liver to body weight ratios, were observed.

Carcinogenicity:

Long term exposure of hydroquinone in animals has demonstrated evidence of carcinogenicity.

Two-year carcinogenicity studies in F344 rats and B6C3F mice dosed with hydroquinone at 0, 25, 50 mg/kg by gavage showed that renal tubule-cell adenomas developed in male rats in 4/55 (7.3%) low-dosed groups (p=0.069) and in 8/55 (14.5%) high-dosed group (p=0.003), compared with 0/55 in the control rats. Hyperplasia was also reported in the high dose group of male rats, with a low incidence and none in the other groups. No renal tumors were detected in the female groups at any dose administered. Hepatocellular adenomas were detected in female mice. The incidences observed in females in both dosed groups (27% and 22%) are significantly above the concurrent vehicle control (4%) and historical controls incidence (2%- 22%). The study concluded that “the study strongly suggested that since hydroquinone has apparent carcinogenic potential for rodents, there is a possibility that it may play a role in human cancer development.” Hydroquinone did not induce a significant number of neoplasms in either the glandular or nonglandular stomach of hamsters fed 0.5% hydroquinone in the diet for 20 weeks or rats fed 0.8% hydroquinone in the diet for 51, 49, or 8 weeks.

In an NTP study, hydroquinone was given to rats orally by gavage five times per week for up to 103 weeks at doses of 25 or 50 mg/kg. The higher dose induced a significant incidence of renal adenomas in males and both doses caused a significant increase in the incidence of mononuclear cell leukemia in females. Mice were dosed with 50 or 100 mg/kg hydroquinone following the same schedule as that used for the rats. The incidence of hepatocellular adenoma was significantly increased in female mice.

NTP concluded that hydroquinone produced “some evidence of carcinogenic activity” for male and female F344/N rats and female B6C3F mice, but “no evidence of carcinogenic activity” for male B6C3F mice in an oral carcinogenicity.

Hydroquinone increased the incidences of mononuclear cell leukemia in female rats. Mononuclear-cell leukemia developed in 15/55 (27%) low-dose group rats (p=0.048) and 22/55 (40%) high-dose group rats (p=0.003), compared with 9/55 (16%) control group rats. The incidence for this neoplasm in the high-dose group exceeds the incidence in the concurrent control group and the incidence in the controls in 45/46 studies that include almost 2500 untreated or water gavage control F344 female.

In another study in the same animals and strains (Shibata et al., 1991) fed a diet containing hydroquinone 0 or 0.8% (calculated intake of 351 mg/kg /day and 368 mg/kg/day for males and females, respectively) for 104 weeks, the development of renal tubule-cell adenomas was confirmed in male rats, but not the hepatocellular adenomas in female mice. In this study leukemia was not reported.

Reproduction, Embryotoxicity and Teratogenicity:

In a study by Skalka (1964), the fertility was reduced by 33% in the males and the number of pregnancies in mated females was reduced by 19% compared with the corresponding results for the control animals. Histological examinations indicated a disruption in sperm production. Diminished content of DNA in sperm heads was also noted.

In 13-week and two-year oral studies in rats and mice, no effects on testicular or epididymal weights or on the histopathology of these organs were observed (NTP, 1989).

Hydroquinone was shown to affect the rat estrus cycle when given parenterally (Rosen & Millman, 1955). Three rats were given 10 mg hydroquinone/day subcutaneously for 11 days, and vaginal smears were used to indicate estrus or diestrus. Following an induction period of about three days, the estrus cycle was interrupted for 5 days, after which normal cycling was observed.

Hydroquinone induced embryotoxicity in chick and rat embryos cultured in vitro, increased fetal resorption rates in pregnant rats fed a total dose of 0.5 g hydroquinone in the diet. However, in other studies of rats and rabbits, oral hydroquinone given at the corresponding gestation periods did not produce embryo-toxic, fetotoxic, or teratogenic effects and in a two consecutive generations study of rats, oral hydroquinone did not adversely affect survival, reproductive parameters, pup weight, sex distribution, gross lesions or microscopic anatomy at doses as high as 150 mg/kg/day.

Fertility was affected after hydroquinone s.c. or gavage administration; hydroquinone prolonged the diestrus period of the sexual cycle in female albino rats; in male rats, hydroquinone decreased weights in testes, epididymides, seminal vesicles and adrenal glands; histological changes in testes indicating disrupted spermiogenesis; and diminished DNA content of sperm heads. It was also reported in one study that reproduction parameters were not affected in female rats fed hydroquinone in the diet prior to mating. No treatment-related effects on reproductive parameters were noted when male mice were exposed to up to 300 mg/kg/day oral hydroquinone for 10 weeks (5 days/wk) and then mated to untreated females (DeCaprio, 1999).

Oral administration of hydroquinone did not produce embryotoxic, fetotoxic, or teratogenic effects in rats, nor did it produce significant adverse reproductive effects in a two-generation study. Using rabbits, various teratogenic/reproductive treatment-related effects were observed at doses of 200-500 mg/kg. All dams dosed with 300 to 500 mg/kg hydroquinone died. Some maternal toxicity was observed at a number of dose concentrations.

Mutagenesis:

Published studies have demonstrated that hydroquinone is a mutagen and a clastogen. Treatment with hydroquinone has resulted in negative results in Salmonella typhimurium TA 100, TA98, TA1535, TA1537 reverse mutation, but it was positive in Salmonella typhimurium TA102 a bacterial strains sensitive to oxidizing mutagens, in a variety of in vitro tests in mammalian cells (chromosomal aberration, sister chromatid exchange, DNA single-strand breaks, aneuploidy, micronucleous, and others) and in the in vivo tests chromosomal aberrations, aneuploidy, and micronucleous in mouse bone marrow after intraperitoneal administered.

Hydroquinone induced SCEs, chromosomal aberrations, and mitotic division aberrations increased the frequency of mitotic crossovers, caused c-mitotic effects, and induced chromosome loss. It was clastogenic for male mouse germ cells and for mouse bone marrow cells. Hydroquinone induced DNA strand breaks and inhibited DNA, nuclear DNA, and mtDNA synthesis in rabbit bone marrow mitochondria. It also inhibited mtDNA transcription synthesis and RNA synthesis.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ERFA HYDROQUINONE
Hydroquinone gel

FOR EXTERNAL USE ONLY

Read this carefully before you start taking **ERFA HYDROQUINONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ERFA HYDROQUINONE.**

What is ERFA HYDROQUINONE used for?
ERFA HYDROQUINONE is used to lighten areas of darkened skin caused by sun exposure, skin damage, pregnancy, medications or age.

Before your doctor prescribes ERFA HYDROQUINONE, they will check your areas of darkened skin to make sure they are not due to a more serious skin condition.

How does ERFA HYDROQUINONE work?
ERFA HYDROQUINONE blocks the formation of melanin in the skin. Melanin is the pigment in skin that gives it a brown color.

What are the ingredients in ERFA HYDROQUINONE?
Medicinal ingredients: hydroquinone
Non-medicinal ingredients: Ammonium hydroxide, butylhydroxytoluene, citric acid anhydrous, disodium edetate, ethanol 96%, glycolic acid, propylene glycol, polyquaternium-10, sodium metabisulfite, sodium sulfite anhydrous, and purified water.

ERFA HYDROQUINONE comes in the following dosage forms:
As a gel, 4% w/w.

Do not use ERFA HYDROQUINONE if you:

- Are allergic to hydroquinone;
- Are allergic to sodium metabisulfite or any of the other ingredients in ERFA HYDROQUINONE;
- Are allergic to any part of the container.
- Are taking any medicines that make your skin more sensitive to light. These include medicines used to prevent or treat malaria, like resorcinol and phenol.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ERFA HYDROQUINONE. Talk about any health conditions or problems you may have, including if you:

- Have asthma.
- Are pregnant or are breast-feeding.

- Have or have had cancer.

Other warnings you should know about:

The safety of topical hydroquinone use during pregnancy or for children has not been studied.

Treatment amount, duration and use:

- Do not apply ERFA HYDROQUINONE on broken skin or on mucous membranes. Mucous membranes are in your nose or mouth and in or around your genitals and anus. Do not apply ERFA HYDROQUINONE to any of these areas. Avoid contact with eyes. In case of contact with eyes, broken skin or mucous membranes, rinse thoroughly with water.
- Do not use ERFA HYDROQUINONE on large areas of skin. Do not apply it more often your doctor tells you to. Too much ERFA HYDROQUINONE may irritate your skin or cause other side effects.
- Do not use ERFA HYDROQUINONE for longer than 2-3 months or the duration recommended by your doctor.

Sun protection:

- You must protect your skin from ultraviolet (UV) light while using ERFA HYDROQUINONE. This includes using sunscreen and wearing clothing that protects your skin from the sun. Use a sunscreen of at least SPF 30 (UVA & UVB) and cover the treated areas with clothing or a wide brimmed hat. This is to prevent your skin from darkening again and to prevent sunburn. ERFA HYDROQUINONE contains ingredients that make your skin more sensitive to light. Use clothing whenever possible to protect from UV light.
- Do not use tanning lamps and tanning beds.
- If you get sunburned, stop using ERFA HYDROQUINONE until your sunburn has healed.
- After stopping ERFA HYDROQUINONE treatment, continue to protect your skin from sunlight.

Monitoring your skin:

- If the skin areas you are treating are not lighter after 3 weeks of applying ERFA HYDROQUINONE, talk to your doctor. Your doctor will need to assess your skin for more serious conditions and decide if you can keep using ERFA HYDROQUINONE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ERFA HYDROQUINONE:

- Any medicines that make your skin more sensitive to light. These include medicines used to prevent or treat malaria, resorcinol and phenol. Other medicines may also make your skin more sensitive to light. If you are not sure if a medicine you take does this, talk to your doctor. You should not use ERFA HYDROQUINONE if you are taking these medicines.
- Products called peroxides. These include benzoyl peroxide and hydrogen peroxide. Benzoyl peroxide is used to treat acne and is often found in topical acne products. Hydrogen peroxide is used to disinfect minor wounds and to bleach hair. You should not use ERFA HYDROQUINONE along with these products since this can change the colour of your skin. If

you get peroxides on your skin at the same time as ERFA HYDROQUINONE, wash your skin with a mild soap and water.

How to use ERFA HYDROQUINONE:

- Use ERFA HYDROQUINONE exactly as your doctor has told you to.
- Follow all instructions given to you by your doctor.

Test for skin sensitivity before use:

- Apply a small amount of ERFA HYDROQUINONE onto your skin.
- Do not apply to skin that has any cracks, cuts or sores on it.
- Check to see how your skin looks 24 hours after you have applied ERFA HYDROQUINONE.
- If your skin is itchy, swollen or has blisters on it where you applied ERFA HYDROQUINONE, do not use it again.

How to use:

- If your skin was not sensitive after the steps above, you can start using ERFA HYDROQUINONE.
- Put a small amount (a pea-sized amount) of ERFA HYDROQUINONE on your fingertip.
- Apply a thin even layer onto the dark spots. Include about a half inch of the normal skin that surrounds your dark spots in your application.
- Lightly rub ERFA HYDROQUINONE into your skin. The medicine should become invisible almost at once. If you can still see it, you are using too much.
- Do not apply ERFA HYDROQUINONE to the corners of your nose, your mouth, eyes, on any mucous membranes or on open wounds. Spread it away from those areas when applying it.
- Keep the treated area uncovered after applying ERFA HYDROQUINONE.
- Wash hands with soap after you have applied ERFA HYDROQUINONE to prevent brown spots on your fingernails.

Usual dose:
The usual dose is a small amount (a pea-sized amount) twice a day, once in the morning and once in the evening. Your doctor may tell you to apply ERFA HYDROQUINONE less often. Your doctor will decide how often and for how long you should use ERFA HYDROQUINONE.

Overdose:

If you think you have used too much ERFA HYDROQUINONE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for a missed dose.

What are possible side effects from using ERFA HYDROQUINONE?

These are not all the possible side effects you may feel when taking ERFA HYDROQUINONE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include skin reactions such as:

- redness
- dryness
- burning
- peeling
- itching
- tingling
- stinging
- increased sensitivity to sunlight and UV light
- increased possibility of sunburn
- acne-like skin eruption

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic reactions: difficulty breathing, difficulty swallowing, fever, hives, itching, rash, swelling of your tongue or throat.			x
Vitiligo (skin condition)**:** white patches or spots on the skin.			x
Neoplasm (abnormal skin growth): new skin patch, growth or mole that was not previously there.			x
Ochronosis (skin condition): blue or black discoloration of the skin, darkening of the skin, raised areas of skin.			x
Skin eruptions: itchy blisters on skin.			x
Skin irritation	x		
Contact dermatitis (skin condition): red rash, itching, dry, cracked or scaly skin, bumps or blisters, swelling, burning or tenderness of the skin.	x		
Chemical burn: redness, burning pain, blisters or black dead skin at site of contact.			x
Scarring	x		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature between 15 - 30°C. Do not freeze. Keep the tube totally sealed to protect it from light. Keep out of the reach and sight of children. Do not use the product if dark coloration is observed, even if it is within the expiry period.

If you want more information about ERFA HYDROQUINONE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.eci2012.net , or by calling 1-800-931-3133.

This leaflet was prepared by ERFA Canada 2012 Inc.

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