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(54) Title: FORMULATIONS OF VITAMIN K ANALOGS FOR TOPICAL USE

(57) Abstract: The present invention provides topical formulations containing a vitamin K analog, e.g., menadione, that deliver a uniform, therapeutically effective concentration of the vitamin K analog to the skin in a vehicle which is stable, non-irritating, non-drying and cosmetically acceptable. These topical formulations are useful for the treatment and prevention of dermatological conditions associated with inflammation, particularly, dermatological conditions resulting from anti-EGFR therapies.



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FORMULATIONS OF VITAMIN K ANALOGS FOR TOPICAL USE

RELATED APPLICATIONS

This application claim priority to U.S. Provisional Application No. 61/069,218,
5 titled “EMULSIONS OF VITAMIN K ANALOGS FOR TOPICAL USE”, filed
March 13, 2008 and to U. S. Provisional Application No. 61/204,939, titled
“EMULSIONS OF VITAMIN K ANALOGS FOR TOPICAL USE”, filed January 13,
2009, the entire contents of which are incorporated herein by this reference.

10 BACKGROUND OF THE INVENTION

Epidermal growth factor (EGF), acting through its receptor EGFR, is a mitogen
and survival factor for keratinocytes and other epithelial cells (Rheinwald *et al.* Nature,
1997; 265:421; Rodeck *et al.* J. Cell Science, 1997; 110:113). It is crucial for the normal
development and physiology of the epidermis. Inhibition of EGFR can result in
15 abnormal proliferation, migration and premature differentiation of basal keratinocytes as
demonstrated by upregulated p27KIP1, KRT1 and STAT3 in the basal layer, and
consequent disruption of the integrity of the skin with the recruitment of inflammatory
cells (Jost *et al.* Eur. J. Dermatol. 2000; 10:505-510; Lacouture, Nat. Rev. Cancer 2006;
6:803-812).

20 Agents that inhibit EGFR have been shown to be active antitumor agents against
a variety of solid tumors including but not limited to colorectal carcinoma, non-small
cell lung cancer, head and neck cancer and malignant gliomas (Conen et al., 2003; Lage
et al., 2003; Lorusso, 2003; Vanhoefer et al., 2004). Clinical benefit, defined as relief of
symptoms or prolongation of survival, has been so far demonstrated with the anti-EGFR
25 antibody cetuximab (Erbix®) and the EGFR tyrosine kinase (TK) inhibitors gefitinib
(Iressa®) and erlotinib (Tarceva®).

In addition, EGFR inhibitors are increasingly being used in a range of tumor
types in combination with standard therapies in an attempt to improve outcome. In
2006, results of a randomized phase III study demonstrated that the addition of the
30 EGFR-targeted IgG1 mAb, cetuximab, to radiotherapy resulted in statistically significant
and clinically meaningful improvements in the duration of locoregional control and
median overall survival versus radiotherapy alone in the treatment of locoregionally

advanced squamous cell carcinoma of the head and neck (Bonner *et al. N. Engl. J. Med.* 2006; 354:567-578).

Although EGFR inhibitors do not cause life threatening toxicities, their use can be associated with the development of skin reactions, including a macular, papular, pustular rash, commonly referred to as acne-like rash (or folliculitis); xerosis; fissures; telangiectasia; hyperpigmentation; and hair and nail changes (Segaert *et al. Ann. Oncol.* 2005; 16:1425-1433). In addition, inflammation is commonly found in the epidermal-dermal junction, accompanied by neutrophilic infiltration and damage to the hair follicles.

The most common skin reaction, the acne-like rash which occurs in 60-70% of patients, is generally distributed in areas rich with sebaceous glands, such as the face, neck and retroauricular area, the shoulders, the upper trunk and the scalp. Main symptoms caused by the skin rash, itching, dryness, and secondary infection, cause discomfort and unfavorable cosmetic changes in many cases. The occurrence and intensity of the rash are clearly dose-related and the median time of occurrence is 10 days after initiation of therapy and peaks after 2-3 weeks. In some cases, the rash can be delayed, and in others flares can occur at each subsequent administration of the EGFR inhibitor. In addition, abnormalities in hair growth especially the scalp and eyelashes have been reported in approximately 20% of patients, and periungual inflammation with tenderness in about 15% (Lacouture, *Nat. Rev. Cancer*, 2006; 6:803-812). About 10% of patients discontinue therapy due to skin toxicity.

There is growing evidence that the skin rash is a surrogate indicator of antitumor efficacy and clinical benefit of anti-EGFR therapy (Cohen *et al. J. Clin. Oncol.*, 2003; 21:1980-1987). Accordingly, increasing dosing of anti-EGFR agents to cause a skin rash may become a common practice and the effective treatment of the skin rash is also becoming of increasing importance. Topical or systemic antibiotics, anti-inflammatory agents, retinoids, topical lubricants, and other types of remedies have been tried in an empirical fashion with poor or inconsistent results. More recently, the topical application of menadione (vitamin K3), an EGFR phosphatase inhibitor, was shown to restore EGFR-mediated signaling in human skin secondary to systemic administration of the EGFR inhibitors, erlotinib and cetuximab (Ling *et al. WO* 2006/113479).

Accordingly, there is a need for effective topical formulations for the treatment and/or prevention of this EGFR-mediated skin conditions including epithelial toxicity associated with anti-EGFR therapy, a condition that is expected to affect more than 150,000 individuals each year in the USA alone.

5

SUMMARY OF THE INVENTION

The present invention demonstrates, *inter alia*, that topical formulations containing a vitamin K analog, *e.g.*, menadione, deliver a uniform, therapeutically effective concentration of the vitamin K analog to the skin in a vehicle which is stable,
10 non-irritating, non-drying and cosmetically acceptable. These topical formulations are useful for the treatment and prevention of dermatological conditions associated with inflammation, particularly, dermatological conditions resulting from anti-EGFR therapies.

Accordingly, in one aspect, the invention provides a topically applicable
15 pharmaceutical formulation suitable for treatment of a dermatological condition comprising a vitamin K analog, a, *i.e.*, one or more, lipophilic component, a, *i.e.*, one or more, gelling agent, a, *i.e.*, one or more, microbiological preservative, and water.

In one embodiment, the vitamin K analog contained in the pharmaceutical formulation of the invention activates EGFR. In another embodiment, the vitamin K
20 analog is menadione, a drug substance for which a monograph exists in the United States Pharmacopeia (USP). In one embodiment, the formulation is ethyl alcohol free.

In related embodiments, the formulation comprises a sufficient amount of the vitamin K analog, or a sufficient composition independent of the vitamin K analog concentration, to deliver a concentration of 0.1 to 1.5 mM of the vitamin K analog to the
25 epidermal skin layer when applied topically, or a concentration of 0.2 to 1.2 mM of the vitamin K analog when applied topically. In other related embodiments, the pharmaceutical formulation comprises from about 0.01% to 10% (w/w) of the vitamin K analog, from about 0.05% to 0.5% (w/w) of the vitamin K analog, from about 0.05% to 0.2% (w/w) of the vitamin K analog, about 0.05% (w/w) of the vitamin K analog, about
30 0.1% (w/w) of the vitamin K analog, or about 0.2% (w/w) of the vitamin K analog.

In another embodiment, the lipophilic component contained in the pharmaceutical formulation of the invention is selected from the group consisting of

isopropyl myristate, caprylic/capric triglyceride, diethyl sebacate, diisopropyl adipate, petrolatum, mineral oil, and cyclomethicone.

In a related embodiment, the formulation comprises from about 1% to about 100% (w/w) of the lipophilic component. In another embodiment, the formulation
5 comprises from about 1% to about 35% (w/w) of the lipophilic component. In yet another embodiment, the formulation comprises from about 3% to about 12% (w/w) of the lipophilic component.

In another embodiment, the pharmaceutical formulation of the invention contains from about 0.1 to 5% (w/w) of a gelling agent. In one embodiment, the gelling agent
10 comprises one or more acrylic acid based polymers (*e.g.*, Carbopol 981, Pemulen TR-1, or combinations thereof).

In another embodiment, the pharmaceutical formulation of the invention comprises from about zero % to 95% (w/w) water. In one embodiment, the formulation comprises from about 60% to 90 % (w/w) water. In another embodiment, the
15 formulation comprises from about 30% to 95 % (w/w) water.

In further embodiments, the pharmaceutical formulation of the invention may contain a microbiological preservative if the formulation contains water. In one embodiment, the preservative is selected from the group consisting of benzyl alcohol, methylparaben and propylparaben. In related embodiments, the formulation contains
20 from about 0.01 to 50% (w/w) of the preservative, or from about 0.01 to 5% (w/w) of the preservative. In other related embodiments, the formulation contains from about 0.1% to 5% benzyl alcohol, about 0.5% to 5%, or about 1% benzyl alcohol.

In still other embodiments, the pharmaceutical formulation of the invention may also contain a neutralizing agent. In related embodiments, the neutralizing agent
25 maintains the pH of the formulation at about 4.0 to 8.0, at about 5.0 to 6.5, or at about 5.5 to 6.0. In another embodiment, the neutralizing agent maintains the pH of the formulation at about 5.5.

In preferred embodiments, the pharmaceutical formulation of the invention is a cream or a lotion. In related embodiments, the formulation is a lotion having a viscosity
30 at room temperature (25°C) of approximately 1,000 to 20,000 cps, approximately 1,000 to 10,000, or approximately 3,000 to 4,000 cps.

In one preferred embodiment, the pharmaceutical formulation comprises: from about 0.01 to 10% (w/w) of menadione; from about 1 to 50% (w/w) of one or more

lipophilic components; from about 0.01 to 5% (w/w) each of two different acrylic acid based polymers; from about 0.03 to 10% (w/w) of a preservative; a neutralizing agent sufficient to maintain a pH of about 4.0 to 7.0; and water.

In another preferred embodiment, the pharmaceutical formulation comprises:
5 from about 0.05 to 2% (w/w) of menadione; from about 3 to 20% (w/w) of one or more lipophilic components; from about 0.1 to 1 % (w/w) of an acrylic acid based polymer; from about 0.5 to 5% (w/w) of a preservative; a neutralizing agent sufficient to maintain a pH of about 4.5 to 6.5; and water.

In another preferred embodiment, the pharmaceutical formulation comprises:
10 about 0.05% to 0.2% (w/w) menadione; about 12% (w/w) isopropyl myristate; about 0.3% (w/w) Pemulen TR-1; about 0.1% (w/w) Carbopol 981; about 1% (w/w) benzyl alcohol; sodium hydroxide sufficient to maintain a pH of about 5.0-6.0; and water.

In another preferred embodiment, the pharmaceutical formulation comprises:
about 0.05% to 0.2% (w/w) menadione; about 3% (w/w) diethyl sebacate; about 0.3%
15 (w/w) Pemulen TR-1; about 0.1% (w/w) Carbopol 981; about 0.3% (w/w) each of methylparaben and propylparaben; sodium hydroxide sufficient to maintain a pH of about 5.5 to 6.0; and water.

In another preferred embodiment, the pharmaceutical formulation comprises:
about 0.05% to 0.2% (w/w) menadione; about 6% (w/w) diisopropyl adipate; about
20 0.3% (w/w) Pemulen TR-1; about 0.1% (w/w) Carbopol 981; about 0.3% (w/w) each of methylparaben and propylparaben; sodium hydroxide sufficient to maintain a pH of about 5.5; and water.

In another preferred embodiment, the pharmaceutical formulation comprises:
about 0.05% to 0.2% (w/w) menadione; about 15% (w/w) diethyl sebacate; about 50%
25 (w/w) isopropyl myristate; and about 35% (w/w) mineral oil.

In another preferred embodiment, the pharmaceutical formulation comprises:
about 0.05% to 0.2% (w/w) menadione; about 15% (w/w) diethyl sebacate; about 10%
(w/w) isopropyl myristate; about 65% (w/w) mineral oil; and about 10% cyclomethicone
5-NF.

30 In a related aspect, the invention also provides a packaged topically applicable pharmaceutical formulation suitable for treatment of a dermatological condition comprising a vitamin K analog, one or more lipophilic components, one or more gelling

agents, one or more preservatives, and water in a light impermeable container. In one embodiment, the formulation is ethyl alcohol free.

In related embodiments of this aspect of the invention, the packaged formulation is chemically stable at a temperature of about 25°C for at least about 3 months, at least
5 about 6 months, at least about 9 months, or at least about 12 months. In one embodiment, the packaged pharmaceutical formulation is chemically stable in the temperature range of about 5°C to 25°C for at least about 3 months, at least about 6 months, at least about 9 months, or for at least about 12 months.

In another embodiment, the container is a compressible tube equipped with a
10 blind end and a plastic cap composed of low-density or high-density polyethylene, polypropylene, or other similar polymers. Preferably the tube is composed of aluminum, and more preferably, the tube further comprises an internal lacquer coating.

In other embodiments, the container has from about a 10 to 200 g capacity, from about a 20 to 150 g capacity, from about 10-100 g, has about 30 g capacity or about 100
15 g capacity.

In still another embodiment, the packaged pharmaceutical formulation of the invention may also comprise an applicator, e.g., and LPDE applicator.

In another aspect, the invention provides a method of treating or preventing a dermatological condition comprising topically administering a therapeutically effective
20 amount of a pharmaceutical formulation comprising a vitamin K analog, one or more lipophilic components, one or more gelling agents and/or dispersing agents, one or more preservatives, water, and other components as deemed appropriate. Alternatively, the formulation may comprise a vitamin K analog in a base of lipophilic components, without added water. The formulations of the invention may contain the vitamin K
25 analog in a dissolved state or as a solid dispersion.

In one embodiment, the pharmaceutical formulation is administered topically at least once daily. In another embodiment, the pharmaceutical formulation is administered topically about one to four times daily. In one embodiment, the formulation is administered for about 3 days or about 4 days. In one embodiment the
30 formulation is administered in about a 7-day cycle. In one embodiment, the formulation is administered in about a 7-day cycle over about a 28-day period.

In one embodiment, the dermatological conditions that may be treated according to the methods of the invention are associated with inflammation of the epidermis including, but not limited to skin rash, psoriasis, eczema, dermatitis, hair loss, and acne.

In a preferred embodiment, the dermatological condition is secondary to an anti-epidermal growth factor receptor (EGFR) therapy such as treatment with an anti-EGFR antibody (e.g., cetuximab) or with an EGFR tyrosine kinase inhibitor (e.g., gefitinib or erlotinib), and includes, but is not limited to, skin rash (e.g., acneform or macro-papular rash), hair follicle dysplasia, interfollicular epidermal hyperplasia, a failure or delay of wound healing and combinations thereof.

10

DETAILED DESCRIPTION

The instant invention is based, at least in part, on the discovery that a vitamin K analog, *e.g.*, vitamin K3 (menadione), is compatible (*e.g.*, physically and chemically stable) with various lipophilic components and incompatible with the majority of hydrophilic components tested. In particular, it has been discovered that formulations containing menadione, lipophilic components, gelling agents, preservatives, and water are capable of delivering therapeutically effective doses of menadione to the skin when topically administered.

Various aspects of the present invention are described in further detail in the following subsections.

I. Topical Formulations Containing Vitamin K Analogs

The topical formulations of the invention may be hydrophobic ointments, hydrophilic ointments, hydrophobic solutions, suspensions, sprays, or foams.

In one embodiment, the topical formulations of the invention are emulsions. A formulation, *e.g.*, a topical emulsion, of the invention, in general, contains a vitamin K analog, a lipophilic component, a gelling agent and water. In one embodiment, the emulsions of the invention are ethyl alcohol free. Additional ingredients of the formulation may include, but are not limited to, preservatives, neutralizing agents, dispersing agents, antioxidants, UV-A and UV-B screening agents, topical anesthetics, polyol prepolymers, and phospholipids.

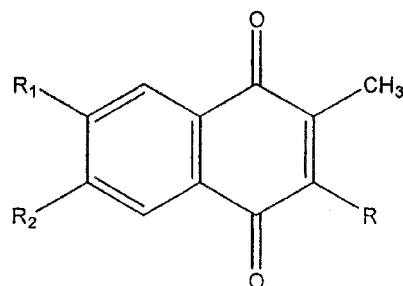
A pharmaceutical formulation, *i.e.*, an emulsion, of the invention is formulated to deliver a therapeutically effective amount of the active ingredient, a vitamin K analog, to the epidermal layers of the skin when topically administered. The emulsion can be made using processes typical for the commercial manufacture of emulsions such as those
5 described in the Examples set forth below. Preferably, the formulation is provided in the form of a cream or lotion and, preferably, is a lotion. In one embodiment, a lotion has the viscosity of approximately 3000 to 4000 cps. In another embodiment, the lotion has the viscosity of approximately 1000 to 10,000 cps.

In certain embodiments, a topical formulation of the invention is formulated to
10 deliver a concentration of from about 0.1 to about 0.5 mM of the vitamin K analog to the epidermal layer of the skin when applied topically, *e.g.*, does not permit penetration of the analog to deeper layers of the skin and/or to enter the circulation. In other embodiments, the formulation is formulated to deliver a concentration from about 0.2 to about 1.2 mM of a vitamin K analog to the epidermal skin layer when applied topically.

Typically, the formulation will comprise from about 0.01% to about 10% (w/w),
15 from about 0.02 to about 2% (w/w), and preferably, from about 0.05 to about 0.5% (w/w) of the vitamin K analog. In one embodiment, the formulation contains from about 0.05 to about 0.2% (w/w) of the vitamin K analog. In one embodiment, the formulation comprises about 0.05% (w/w) of the vitamin K analog. In one embodiment, the
20 formulation comprises about 0.1% (w/w) of the vitamin K analog. In one embodiment, the formulation comprises about 0.2% (w/w) of the vitamin K analog.

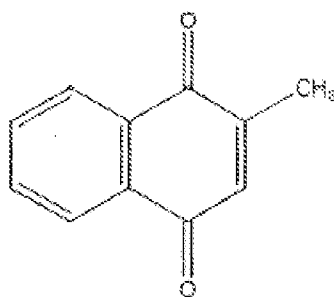
Vitamin K analogs that may be used in the formulation of the invention include any member of the vitamin K group, *i.e.*, the group of naphthoquinone derivatives which can activate EGFR, Akt and/or Stat-3, or combinations thereof. As used herein, to
25 "activate" EGFR, Akt and/or Stat-3 means to increase the phosphorylated form of EGFR, Akt and/or Stat-3. Examples of vitamin K analogs include, but are not limited to, vitamin K1 (2-methyl-3-phytyl-1,4-naphthoquinone), vitamin K2 (2-methyl-3-hexaprenyl-1,4-naphthoquinone; menaquinone), menadione (vitamin K3; 2-methyl-1,4-naphthoquinone), vitamin K4 (1,4-diacetoxy-2-methylnaphthalene), vitamin K5 (4-amino-2-methyl-1-naphthalenol), vitamin K6, vitamin K7 (3-methyl-4-amino-1-naphthol hydrochloride), menadione sodium bisulfite; menadione dimethylpyrimidinol bisulfite, analogs of the vitamin K group members having similar function, including but
30 not limited to, dihydrovitamin K, menaquinone-4, menaquinone-6, menaquinone-7,

menadiol, menadiol sodium diphosphate, menadiol diacetate, and menadoxime and its related salts; and compounds having the structure:

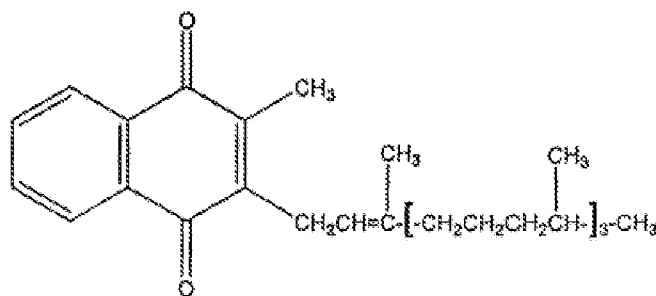


where R = H or a saturated or unsaturated aliphatic hydrocarbon; and R1 and R2 H or
 5 CH3 which can activate EGFR, Akt and/or Stat-3.

In one embodiment, menadione is used in the formulation of the invention.
 menadione has the structure:



In another embodiment, the formulation of the invention contains Vitamin K1.
 10 Vitamin K1 has the structure:



Preferred forms of vitamin K1 are the trans isomer of vitamin K1 or an admixture of the trans and cis isomers, since the cis isomer has little or no biological activity (Matschiner et al., 1972). Vitamin K1 is present in many green leafy plants and vitamin K2 is
 15 produced by many intestinal bacteria. Vitamins K3, K4, K5, K6, and K7 are synthetic analogs. Processes have been described for preparing vitamin K analogs, e.g., U.S.

Patent Nos. 4,374,775, 4,906,411, 5,412,124, 5,637,741, 5,770,774, and 6,579,994, and Sah (1949-50). Vitamins K1, K2 and K3 are available, e.g., from Sigma-Aldrich.

The lipophilic component is provided in the formulation in an amount sufficient to enhance the skin penetration of the vitamin K analog. In certain embodiments, the formulation comprises from about 1 to about 100% of a lipophilic component or a combination of lipophilic components. In other embodiments, the formulation comprises from about 1% to about 35% (w/w), from about 3% to about 15% (w/w), or from about 6% to 12% (w/w) of the lipophilic component. In other embodiments, the formulation comprises about 3% (w/w), about 5% (w/w), about 6% (w/w), about 10% (w/w), about 12% (w/w) or about 15% (w/w) of the lipophilic component.

Lipophilic components that may be used in the topical formulation of the invention are commercially available and include, but are not limited to, polycarbons, e.g., mineral oils and emulsifying wax; petrolatum, synthetic oils, e.g., isopropyl myristate, diethyl sebacate, diisopropyl adipate, caprylic/capric triglyceride; octyldodecyl, isostearyl isostearate, decyl oleate, isopropyl palmitate; and silicone oils, e.g., cyclopentasiloxane, cyclohexasiloxane, cyclotetrasiloxane, dimethicone; vegetable oils, e.g., linseed oil, tung oil, castor oil, peanut oil, olive oil, almond oil; or combinations thereof. In a preferred embodiment, the lipophilic component is selected from the group consisting of isopropyl myristate, diethyl sebacate, diisopropyl adipate, caprylic/capric triglyceride and combinations thereof.

The topical formulation of the invention further comprises one or more gelling agents, typically at a concentration from about 0.1 to 5% (w/w). The term "gelling agent" as used herein, is a substance which thickens and modifies the viscosity of a liquid vehicle to provide ease and uniformity of application. In some cases, high molecular weight gelling agents may control the rate of skin absorption of the drug by a type of controlled release process. In addition, gelling agents may act as emulsion formers and emulsion stabilizers, e.g., as dispersing agents (*i.e.*, to improve the separation of particles and to prevent settling or clumping).

Pharmaceutically acceptable gelling agents employed in the topical formulation of the invention are commercially available and include, but are not limited to, starch, cellulose derivatives, acrylic derivatives, magnesium-aluminum silicates, xanthan gum and colloidal silica, or combinations thereof.

In some embodiments, the gelling agent is a cellulose derivative, such as, methylcelluloses (Methocel, Metolose), ethylcelluloses (Ethocel, Aquacoat[®]), hydroxypropylmethylcelluloses (Kenal, Methocel, Hypromelose), hydroxyethylcelluloses (Cellosize, Natrosol), hydroxypropylcelluloses (Klucel),
5 carboxymethylcelluloses, cross-linked or not, in sodium or calcium form (Akucell, Nymcel, Tylose CB, Croscarmellose, Acdisol) or combinations thereof.

In other embodiments, the gelling agent is an acrylic derivative, e.g., a carbomer or acrylic based polymer. In preferred embodiments, the acrylic based polymer is a Carbopol[®] polymer, , e.g., Carbopol[®] 71G, Carbopol[®] 971P NF, Carbopol[®] 980 NF,
10 Carbopol[®] 981 NF and Carbopol[®] 941 NF. In certain embodiments, the acrylic based polymer is a Pemulen[®] polymeric emulsifier, e.g., Pemulen[®] TR-1 NF or Pemulen[®] TR-2 NF, or combinations thereof. In one preferred embodiment, the gelling agent is a combination of Carbopol[®] 981 NF and Pemulen[®] TR-1 NF.

The topical formulation of the invention further comprises water, preferably
15 purified, to act as a carrier to yield a formulation that is cosmetically acceptable and moisturizing. Typically, the formulation comprises from about 30 to 95% (w/w) water or about 60 to 90% (w/w) water.

In further embodiments, a neutralizer or buffer may be added to stabilize the pH of the formulation to increase the viscosity to an acceptable level. Examples of
20 neutralizing agents include, but are not limited to, sodium hydroxide, potassium hydroxide and triethanolamine. In related embodiments, sufficient neutralizer is added to the formulation to maintain a pH of about 4.0 to 8.0, from about 5.0 to 6.5, or from about 5.0 to 6.0. In another embodiment, sufficient neutralizer is added to maintain a pH of about 5.5.

In other embodiments, a preservative may be included in the formulation of the present invention to prevent microorganism overgrowth with time. In certain
25 embodiments, the preservative is present in the formulation in a w/w amount of from about 0.01 to about 50%, preferably in an amount of from 0.01 to 5%, more preferably in an amount from about 0.5% to 5%. In one embodiment, the formulation contains
30 about 1% (w/w) of the preservative.

Any preservative known to those skilled in the art and not otherwise deleterious to the formulation may be used. Examples of suitable preservatives that include, but are

not limited to, alkyl alcohols (e.g., benzyl alcohol); parabens, (e.g., butyl paraben, propyl paraben) their salts and esters; benzoic acid, its salts and its esters; sorbic acid and its salts; triclosan; imidazolidinyl urea; phenoxyethanol; DMDM hydantoin; diazolidinyl urea and chlorphenesin butylated hydroxytoluene, disodium edetate, citric acid; or
5 combinations thereof. In one preferred embodiment, the preservative included in the formulation is benzyl alcohol.

Additional components that may be included in the topical formulations of the invention include UVA and UVB filters such as benzophenone-3, butyl methoxydibenzoyl methane, octocrylene, octyl methoxycinnamate, 4-methylbenzylidene
10 camphor, octyl salicylate, terephthalylidene dicamphor sulfonic acid and drometrizole trisiloxane; colorants such as lipophilic colorants, hydrophilic colorants, pigments and mother-of-pearl conventionally used in cosmetic or dermatological compositions, topical anesthetics (e.g., benzocaine, butamben, dibucaine, lidocaine, oxybuprocaine, pramoxine, proparacaine, proxymetacaine, and tetracaine), polyol prepolymers (e.g., a
15 degradable biocompatible material, e.g., artificial skin), and phospholipids, and their mixtures.

II. Packaging

The topical formulation of the invention may be conveniently packaged using
20 any light impermeable commercial container (e.g., dark glass, plastic or aluminum) suitable for topical administration including, but not limited to, cans with spray pumps, bottles, jars, vials, tubes and single use packets, which are capable of maintaining the chemical stability of the active ingredient, a vitamin K analog, for at least 12 months at 25°C or at refrigeration (at 4°C). The containers can also be provided with a cap and
25 means for dispensing the topical formulation, e.g., a pump or applicator.

In certain embodiments, the container is a compressible, e.g., can be readily compressed to extrude the topical formulation by an individual with average strength, including but not limited to flexible plastic and aluminum tubes, and flexible unit-dose foil pouches. In one preferred embodiment, the container is an aluminum tube, more
30 preferably, with an internal protective coating (e.g., a lacquer coating) as described in the following Examples.

Typically, the pharmaceutical formulation of the invention is provided in a container having a capacity from about 10-150 g, 20-120, 10 to 200 g or from about 20

to 150 g. In one embodiment, the pharmaceutical formulation is provided in an aluminum tube having a 30 g capacity. In a preferred embodiment, the pharmaceutical formulation is provided in an aluminum tube having a 100 g capacity.

5 **III. Methods of Treatment and/or Prevention**

The invention further provides methods of treating a dermatological condition comprising administering to a patient a therapeutically effective amount of the topical formulation described herein.

10 The term "treating" as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing, either partially or completely, one or more conditions or symptoms associated with a dermatological condition. The term "treatment" as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

15 Similarly, the phrase "therapeutically effective amount" refers to the amount of the topical formulation of the invention capable of treating the dermatological condition. The dose and frequency of administration will depend on the type and severity of the dermatological condition being treated and the size of the affected area. A therapeutically effective amount of the formulation can be administered in single or multiple doses over a period of days, weeks or months as needed to treat the condition.

20 The dose and frequency of administration can also be adjusted up or down by the prescribing physician depending on the degree of responsiveness to the treatment by the particular patient. Typically, the topical formulation of the invention is administered at least once a day and in one embodiment, the formulation is administered between one and four times per day.

25 The term "dermatological condition" as used herein refers to diseases or disorders associated with inflammation of the skin (e.g., epidermis or dermis) including, but not limited to, rashes, eczema, psoriasis, dermatitis, keratosis, acne and epithelial toxicity caused by administration to a patient of a dose (single or divided) or series of doses (e.g., a course of treatment) of an EGFR inhibitor useful in treating cancer.

30 As used herein, the term "epithelial toxicity" refers to an abnormality or dysfunction of the epithelium manifested in a patient receiving anti-EGFR therapy by one or more symptoms or conditions including, but not limited to skin rash, *e.g.*,

macular, papular, pustular rash, commonly referred to as acne-like rash (or folliculitis); seborrheic dermatitis-like rash; xerosis; fissures; telangiectasia; hyperpigmentation; hair atrophy or loss; hair follicle dysplasia; interfollicular epidermal hyperplasia; diffuse erythema with follicular papulopustules; oedematous facial erythema; periungual (the
5 area that surrounds the nail) alterations; and a failure to heal or a delayed healing after injury.

As used herein, the term "patient" or "subject" preferably refers to a human suffering from or at risk of suffering from a dermatological complaint. However, the term "patient" can also refer to non-human animals, preferably mammals such as dogs,
10 cats, horses, cows, pigs, sheep and non-human primates, among others. Preferably, the patient is a human that is being treated or has received treatment with an EGFR inhibitor.

As used interchangeably herein, the terms "EGFR inhibitor" and "anti-EGFR therapy" refer to any EGFR inhibitor that is currently known in the art or that will be
15 identified in the future, and includes any chemical entity that, upon administration to a patient, results in inhibition of a biological activity associated with activation of the EGFRs in the patient, including any of the downstream biological effects otherwise resulting from the binding to an EGFR of its natural ligand. Such EGFR inhibitors include any agent that can block EGFR activation or any of the downstream biological
20 effects of EGFR activation that are relevant to treating cancer in a patient. Such an inhibitor can act by binding directly to the intracellular domain of the receptor and inhibiting its kinase activity. Alternatively, such an inhibitor can act by occupying the ligand binding site or a portion thereof of the EGFR receptor or a portion thereof, thereby making the receptor inaccessible to its natural ligand so that normal biological
25 activity is prevented or reduced. EGFR inhibitors include but are not limited to low molecular weight inhibitors, antibodies or antibody fragments, antisense constructs and ribozymes.

Examples of EGFR inhibitors include but are not limited to those classified in the art as quinazoline EGFR inhibitors, pyrido-pyrimidine EGFR inhibitors, pyrimido-
30 pyrimidine EGFR inhibitors, pyrrolo-pyrimidine EGFR inhibitors, pyrazolo-pyrimidine EGFR inhibitors, phenylamino-pyrimidine EGFR inhibitors, oxindole EGFR inhibitors, indolocarbazole EGFR inhibitors, phthalazine EGFR inhibitors, isoflavone EGFR inhibitors, quinalone EGFR inhibitors, and tyrphostin EGFR inhibitors.

Non-limiting examples of low molecular weight EGFR include any of the EGFR inhibitors described in the following patent publications, and all pharmaceutically acceptable salts and solvates of said EGFR inhibitors: European Patent Application EP 520722, published Dec. 30, 1992; European Patent Application EP 566226, published 5 Oct. 20, 1993; PCT International Publication WO 96/33980, published Oct. 31, 1996; U.S. Pat. No. 5,747,498, issued May 5, 1998; PCT International Publication WO 96/30347, published Oct. 3, 1996; European Patent Application EP 787772, published Aug. 6, 1997; PCT International Publication WO 97/30034, published Aug. 21, 1997; PCT International Publication WO 97/30044, published Aug. 21, 1997; PCT 10 International Publication WO 97/38994, published Oct. 23, 1997; PCT International Publication WO 97/49688, published Dec. 31, 1997; European Patent Application EP 837063, published Apr. 22, 1998; PCT International Publication WO 98/02434, published Jan. 22, 1998; PCT International Publication WO 97/38983, published October 23, 1997; PCT International Publication WO 95/19774, published Jul. 27, 1995; 15 PCT International Publication WO 95/19970, published Jul. 27, 1995; PCT International Publication WO 97/13771, published Apr. 17, 1997; PCT International Publication WO 98/02437, published Jan. 22, 1998; PCT International Publication WO 98/02438, published Jan. 22, 1998; PCT International Publication WO 97/32881, published Sep. 12, 1997; German Application DE 19629652, published Jan. 29, 1998; PCT 20 International Publication WO 98/33798, published Aug. 6, 1998; PCT International Publication WO 97/32880, published Sep. 12, 1997; PCT International Publication WO 97/32880 published Sep. 12, 1997; European Patent Application EP 682027, published Nov. 15, 1995; PCT International Publication WO 97/02266, published January 23, 1997; PCT International Publication WO 97/27199, published Jul. 31, 1997; PCT International 25 Publication WO 98/07726, published Feb. 26, 1998; PCT International Publication WO 97/34895, published Sep. 25, 1997; PCT International Publication WO 96/31510, published Oct. 10, 1996; PCT International Publication WO 98/14449, published Apr. 9, 1998; PCT International Publication WO 98/14450, published Apr. 9, 1998; PCT International Publication WO 98/14451, published Apr. 9, 1998; PCT International 30 Publication WO 95/09847, published Apr. 13, 1995; PCT International Publication WO 97/19065, published May 29, 1997; PCT International Publication WO 98/17662, published Apr. 30, 1998; U.S. Pat. No. 5,789,427, issued Aug. 4, 1998; U.S. Pat. No. 5,650,415, issued Jul. 22, 1997; U.S. Pat. No. 5,656,643, issued Aug. 12, 1997; PCT

International Publication WO 99/35146, published Jul. 15, 1999; PCT International Publication WO 99/35132, published Jul. 15, 1999; PCT International Publication WO 99/07701, published Feb. 18, 1999; and PCT International Publication WO 92/20642 published Nov. 26, 1992. Additional non-limiting examples of low molecular weight
5 EGFR inhibitors include any of the EGFR inhibitors described in Traxler, P., 1998, Exp. Opin. Ther. Patents 8(12):1599-1625.

Specific preferred examples of low molecular weight EGFR inhibitors include [6,7-bis(2-methoxyethoxy)-4-quinazolin-4-yl]-(3-ethynylphenyl)amine (U.S. Pat. No. 5,747,498 issued May 5, 1998 and Moyer et al., 1997, *supra*); CI-1033 and PD183805
10 (Sherwood et al., 1999, Proc. Am. Assoc. Cancer Res. 40:723); and ZD1839 (Woodburn et al., 1997, Proc. Am. Assoc. Cancer Res. 38:633).

Antibody-based EGFR inhibitors include any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Non-limiting examples of antibody-based EGFR inhibitors include those described in
15 Modjtahedi, H., et al., 1993, Br. J. Cancer 67:247-253; Teramoto, T., et al., 1996, Cancer 77:639-645; Goldstein et al., 1995, Clin. Cancer Res. 1:1311-1318; Huang, S. M., et al., 1999, Cancer Res. 59:1236-1243. Thus, the EGFR inhibitor can be monoclonal antibody Mab E7.6.3 (Yang, 1999 *supra*), or Mab C225 (ATCC Accession No. HB-8508), or an antibody or
20 antibody fragment having the binding specificity thereof.

In additional embodiments, the active compounds of the invention can be co-administered with other agents. For example, additional treatments include oral or topical anti-inflammatory or antibiotic medications, sunscreens (e.g., UV-A and UV-B filtering agents), analgesic agents active topically, and the like. The additional agents
25 can be administered either as part of the topical formulation or in a separate pharmaceutical composition. The additional agents can be administered prior to, at the same time, or subsequent to administration of the topical formulation of the invention.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent
30 applications cited throughout this application are hereby incorporated by reference.

EXAMPLE 1 - Menadione Solubility

This study focused on evaluating the solubility properties of menadione in hydrophilic and lipophilic excipients used in topical pharmaceutical products. Initially, solubility studies were conducted in single solvents. The solubility of menadione in the selected solvents is presented in Table 1.

5

Table 1 - Estimated Solubility of Menadione in Single Solvents

Lab Reference	Solvent	(% w/w)
2368-3A	Benzyl Alcohol	Greater than 10%
2368-5A	Dimethyl Isosorbide	Greater than 10%
2368-4A	Diethyl Sebacate	8 to 10%
2368-5B	Diethylene Glycol Monoethylether (Transcutol)	5 to 7%
2368-3B	Caprylic / Capric Triglyceride	4 to 5%
2368-4B	Diisopropyl Adipate	4 to 5%
2368-11B	Ethyl Alcohol (200 proof)	2 to 4%
2368-24A	Polyethylene Glycol 200	2 to 4%
2368-25A	Polyethylene Glycol 400	Greater than 2%
2368-6A	Isopropyl Myristate	2 to 3%
2368-7A	Oleic Acid	2 to 3%
2368-7B	Oleyl Alcohol	2 to 3%
2368-9B	PPG-3 Myristyl Ether	2 to 3%
2368-8A	Peanut Oil	1.5 to 2%
2368-10B	Isopropyl Alcohol	1 to 2%
2368-6B	Octyl Dodecanol	1 to 2%
2368-8B	Propylene Glycol	Less than 1%
2368-42A	Mineral Oil	Less than 0.1%
2368-9A	Purified Water	Less than 0.04%

Based on the single solvent solubility data, a menadione compatibility study with
 10 selected solvents was conducted. Solutions containing 1% w/w of menadione were prepared, packaged in borosilicate clear glass vials, wrapped in aluminum foil and stored at 5°C (dark), 25°C (dark), and 40°C (dark) for a period of 1 month. The physico-chemical properties of the 1% menadione single solvent solutions are presented in: Table 2.

Table 2 - Menadione Compatibility with Single Solvent Systems

Solvent System	Pull Point	Condition	Description	Assay by HPLC
1% Menadione in Benzyl Alcohol	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Conforms	0.97
		25 °C / dark	Conforms	0.97
		40 °C / dark	Conforms	0.97
1% Menadione in Caprylic/Capric Triglyceride	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Conforms	0.97
		25 °C / dark	Conforms	0.98
		40 °C / dark	Conforms	0.98
1% Menadione in Diethyl Sebacate	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Conforms	1.00
		25 °C / dark	Conforms	1.01
		40 °C / dark	Conforms	1.00
1% Menadione in Diisopropyl Adipate	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Conforms	0.98
		25 °C / dark	Conforms	0.98
		40 °C / dark	Conforms	0.98
1% Menadione in Dimethyl Isosorbide	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Deepening in Color	N.T
		25 °C / dark	Deepening in Color	N.T
		40 °C / dark	Brownish solution	N.T
1% Menadione in Transcutol	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Deepening in Color	N.T
		25 °C / dark	Deepening in Color	N.T
		40 °C / dark	Brownish solution	N.T
1% Menadione in Isopropyl Myristate	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Conforms	1.00
		25 °C / dark	Conforms	1.00
		40 °C / dark	Conforms	1.00
1% Menadione in Polyethylene Glycol 400	T ₀	Initial	Clear yellow solution	N.T
	1 Month	5 °C / dark	Brown solution	N.T
		25 °C / dark	Brown/orange solution	N.T
		40 °C / dark	Red solution	N.T

N.T = Not Tested

- 5 As shown in Table 2, menadione was deemed compatible with the selected solvents (i.e. caprylic/capric triglyceride, diethyl sebacate, diisopropyl adipate, and isopropyl myristate) as demonstrated by the solutions retaining their physical appearance and their chemical potency assessed by HPLC after one (1) month of storage at 5°C (dark), 25°C (dark), and 40°C(dark). In contrast, dimethyl isosorbide, transcutol and

polyethylene glycol 400 showed signs of incompatibility with menadione as discoloration of the tested solutions were reported in all of the conditions evaluated.

EXAMPLE 2 - Formulation Development

- 5 The objective during formulation development was to develop a topical formulation with the following properties:
- If possible, a formulation not containing Ethyl Alcohol
 - If possible, compendial formulation components
 - Vehicle composed of excipients present in topical products previously approved by
 - 10 FDA, as demonstrated by the excipient being listed on FDA's Inactive Ingredient Guide
 - Chemically stable
 - Physically stable
 - Highly spreadable and cosmetically elegant
 - Pharmaceutically acceptable attributes
 - 15 • Well preserved product
 - Delivers a target Epidermal Menadione Concentration: 0.1 – 0.5 mM

Formulation Prototypes

Based on the objective of delivering a concentration of 0.1 – 0.5 mM menadione to the epidermal layers, and with the assumption that approximately 2 to 10% of the product's applied dose reaches the target area, a target drug concentration of 0.2% w/w in the formulation was selected (0.2% is equal to approximately 12 mM, therefore the estimated epidermal delivery of 2-10% would be equal to an epidermal concentration of approximately 0.2 – 1.2 mM).

25 Formulations with the target drug concentration of 0.2% w/w, were initially developed and various forms were examined. The investigation consisted of evaluating aqueous emulsions and non-aqueous formulations. Formulations with different emulsifying agents and preservatives were also examined.

The compositions of prototype formulations are presented in Table 3.

30

Table 3 Composition of Menadione Prototype Formulations

Ingredients	% w/w											
	1	2	3	4	5	6	7	8	9	10	11	12
Menadione, USP	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.4	0.2	0.2
Diethyl Sebacate	3.0	----	----	----	----	10.0	10.0	10.0	10.0	10.0	15.0	15.0
Diisopropyl Adipate	----	6.0	----	----	----	----	----	----	----	----	----	----
Isopropyl Myristate, NF	----	----	12.0	12.0	12.0	----	----	----	----	----	50.0	10.0
White Petrolatum, USP	----	----	----	----	----	5.0	5.0	5.0	----	5.0	----	----
Light Mineral Oil, NF	----	----	----	----	----	----	----	----	----	----	34.8	64.8
Cyclomethicone 5-NF	----	----	----	----	----	----	----	----	----	----	----	10.0
Brij 72	----	----	----	----	----	3.5	3.5	----	3.5	3.5	----	----
Brij 721	----	----	----	----	----	1.5	1.5	----	1.5	1.5	----	----
Emulsifying Wax	----	----	----	----	----	----	----	12.0	----	----	----	----
Pemulen TR-1, NF	0.3	0.3	0.3	0.3	0.3	----	----	----	----	----	----	----
Carbopol 981, NF	0.1	0.1	0.1	0.1	0.1	0.1	0.1	----	----	----	----	----
Methylparaben, NF	0.17	0.17	0.17	----	----	----	0.17	0.17	0.17	0.17	----	----
Propylparaben, NF	0.03	0.03	0.03	----	----	----	0.03	0.03	0.03	0.03	----	----
Benzyl Alcohol, NF	----	----	----	1.0	1.0	1.0	----	----	----	----	----	----
Propylene Glycol, USP	----	----	----	----	5.0	----	----	----	----	----	----	----
4% NaOH Solution	q.s. pH 5.0-6.0						----	----	----	----	----	----
Sodium Phosphate Monobasic	----	----	----	----	----	----	q.s. pH 5.0-6.0				----	----
Sodium Phosphate Dibasic	----	----	----	----	----	----	q.s. pH 5.0-6.0				----	----
Purified Water	q.s. ad 100										----	----

The prototype formulations were compounded under yellow light and packaged

5 in borosilicate clear glass vials. Vials designated to be protected from light were wrapped with aluminum foil. All vials were stored at 5°C (dark), 25°C (dark), 25°C (ambient light) and 40°C (dark) for a period of up to 6 months to assess the stability of these formulation prototypes. Each formulation also underwent a freeze thaw study for 1

10 month (approximately 4 cycles per month between -20°C and ambient room temperature) after which each formulation was visually inspected.

The physical and chemical stability results for each prototype formulation are shown in Table 4 to Table 15.

Table 4- Physical & Chemical Stability of Prototype 1

Prototype 1	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.4	3,800	101.4
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.4	3,800	101.4
t = 1 mo	Conforms	5.5	3,600	103.0
t = 3 mo	Conforms	5.4	3,800	101.0
t = 6 mo	Conforms	5.3	3700	98.8
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.2	3,800	98.8
t = 1 mo	Color Deepening / Phase Separation	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.2	3,800	98.8
t = 1 mo	Conforms	5.4	3,500	104.5
t = 3 mo	Conforms	5.4	3,600	101.6
t = 6 mo	Does not conform ²	5.4	3,500	98.5
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.2	3,800	98.8
t = 1 mo	Conforms	5.4	3,500	105.7
t = 3 mo	Color Deepening	5.4	2,800	99.8
t = 6 mo	Does not conform ²	N.T	2,100	96.2

N.T = Not Tested

¹ Viscosity Parameters: Spindle 27, Speed 30 rpm² Large, dark oil droplets observed

Table 5 - Physical & Chemical Stability of Prototype 2

Prototype 2	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.5	3,600	100.5
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.5	3,600	100.5
t = 1 mo	Conforms	5.5	3,300	100.7
t = 3 mo	Conforms	5.5	3,500	99.4
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.5	3,600	100.5
t = 1 mo	Color Deepening / Phase Separation	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.5	3,600	100.5
t = 1 mo	Conforms	5.5	3,300	101.2
t = 3 mo	Conforms	5.5	3,300	98.0
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.5	3,600	100.5
t = 1 mo	Conforms	5.5	3,000	100.2
t = 3 mo	Color Deepening	5.5	2,700	96.3

N.T = Not Tested

¹Viscosity Parameters: Spindle 27, Speed 30 rpm

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Table 6 - Physical & Chemical Stability of Prototype 3

Prototype 3	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.5	4,200	101.6
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.5	4,200	101.6
t = 1 mo	Conforms	5.4	3,800	99.3
t = 3 mo	Conforms	5.5	4,100	97.9
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.5	4,200	101.6
t = 1 mo	Color Deepening / Phase Separation	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.5	4,200	101.6
t = 1 mo	Conforms	5.4	3,800	100.8
t = 3 mo	Conforms	5.5	4,000	97.7
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.5	4,200	101.6
t = 1 mo	Conforms	5.4	3,900	98.7
t = 3 mo	Color Deepening	5.5	3,200	97.7

N.T = Not Tested

¹Viscosity Parameters: Spindle 27, Speed 30 rpm

Table 7 - Physical & Chemical Stability of Prototype 4

Prototype 4	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Yellow lotion	5.2	3,800	98.8
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Yellow lotion	5.2	3,800	98.8
t = 1 mo	Conforms	5.4	3,100	98.2
t = 3 mo	Conforms	5.5	3,600	98.1
t = 6 mo	Conforms	5.4	3,600	96.1
Interval	25 °C Ambient Light			
t = 0 mo	Yellow lotion	5.2	3,800	98.8
t = 1 mo	Heterogeneous	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Yellow lotion	5.2	3,800	98.8
t = 1 mo	Conforms	5.4	3,000	99.5
t = 3 mo	Conforms	5.5	3,400	96.5
t = 6 mo	Conforms	5.4	3,300	95.6
Interval	40 °C dark			
t = 0 mo	Yellow lotion	5.2	3,800	98.8
t = 1 mo	Slight color deepening	5.4	2,600	97.1
t = 3 mo	Thin, deepening in color	5.5	2,500	96.4
t = 6 mo	Thin, deepening in color	5.4	1,800	94.7

N.T = Not Tested

¹Viscosity Parameters: Spindle 27, Speed 30 rpm

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Table 8 - Physical & Chemical Stability of Prototype 5

Prototype 5	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.6	3,900	101.5
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.6	3,900	101.5
t = 1 mo	Conforms	5.6	3,100	98.5
t = 3 mo	Conforms	5.6	3,900	96.8
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.6	3,900	101.5
t = 1 mo	Color Deepening / Phase Separation	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.6	3,900	101.5
t = 1 mo	Conforms	5.6	3,000	99.2
t = 3 mo	Conforms	5.6	3,700	95.7
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.6	3,900	101.5
t = 1 mo	Slight color deepening	5.6	3,100	96.8
t = 3 mo	Thin, deepening in color	5.6	3,100	84.1

N.T = Not Tested

¹Viscosity Parameters: Spindle 27, Speed 30 rpm

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Table 9 - Physical & Chemical Stability of Prototype 6

Prototype 6	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	6.0	460	100.9
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	6.0	460	100.9
t = 1 mo	Conforms	6.4	390	95.1
t = 3 mo	Conforms	6.1	580	98.5
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	6.0	460	100.9
t = 1 mo	Color Deepening / Phase Separation	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	6.0	460	100.9
t = 1 mo	Conforms	6.2	450	98.1
t = 3 mo	Conforms	6.1	440	98.0
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	6.0	460	100.9
t = 1 mo	Conforms	6.3	360	95.9
t = 3 mo	Phase Separation	N.T	N.T	N.T

N.T = Not Tested

¹Viscosity Parameters: Spindle 21, Speed 60 rpm

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Table 10 - Physical & Chemical Stability of Prototype 7

Prototype 7	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.8	390	103.0
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.8	390	103.0
t = 1 mo	Conforms	5.9	450	99.8
t = 3 mo	N.T	N.T	N.T	N.T
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.8	390	103.0
t = 1 mo	Phase Separation	N.T	N.T	N.T
t = 3 mo	N.T	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.8	390	103.0
t = 1 mo	Conforms	5.9	450	100.6
t = 3 mo	N.T	N.T	N.T	N.T
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.8	390	103.0
t = 1 mo	Phase Separation	N.T	N.T	N.T
t = 3 mo	N.T	N.T	N.T	N.T

N.T = Not Tested

¹Viscosity Parameters: Spindle 21, Speed 60 rpm

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Table 11 - Physical & Chemical Stability of Prototype 8

Prototype 8	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.9	12,200	102.1
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.9	12,200	102.1
t = 1 mo	Conforms	5.9	12,000	92.9
t = 3 mo	Conforms	5.9	12,000	102.8
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.9	12,200	102.1
t = 1 mo	Color deepening	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.9	12,200	102.1
t = 1 mo	Conforms	5.9	12,000	103.2
t = 3 mo	Conforms	5.8	12,000	101.2
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.9	12,200	102.1
t = 1 mo	Conforms	5.8	4,000	98.2
t = 3 mo	Slight color change	5.6	8,600	102.8

N.T = Not Tested

¹Viscosity Parameters: Spindle 14, Speed 60 rpm

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Table 12 - Physical & Chemical Stability of Prototype 9

Prototype 9	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.8	320	105.7
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.8	320	105.7
t = 1 mo	Conforms	5.9	360	103.8
t = 3 mo	N.T	N.T	N.T	N.T
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.8	320	105.7
t = 1 mo	Phase Separation	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.8	320	105.7
t = 1 mo	Conforms	5.8	410	102.8
t = 3 mo	N.T	N.T	N.T	N.T
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.8	320	105.7
t = 1 mo	Phase Separation	N.T	N.T	N.T
t = 3 mo	N.T	N.T	N.T	N.T

N.T = Not Tested

¹Viscosity Parameters: Spindle 21, Speed 60 rpm

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Table 13 - Physical & Chemical Stability of Prototype 10

Prototype 10	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Light yellowish lotion	5.8	350	100.5
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Light yellowish lotion	5.8	350	100.5
t = 1 mo	Conforms	5.8	360	93.3
t = 3 mo	N.T	N.T	N.T	N.T
Interval	25 °C Ambient Light			
t = 0 mo	Light yellowish lotion	5.8	350	100.5
t = 1 mo	Phase Separation	N.T	N.T	N.T
Interval	25 °C dark			
t = 0 mo	Light yellowish lotion	5.8	350	100.5
t = 1 mo	Conforms	5.8	340	99.9
t = 3 mo	N.T	N.T	N.T	N.T
Interval	40 °C dark			
t = 0 mo	Light yellowish lotion	5.8	350	100.5
t = 1 mo	Phase Separation	N.T	N.T	N.T
t = 3 mo	N.T	N.T	N.T	N.T

N.T = Not Tested

¹Viscosity Parameters: Spindle 21, Speed 60 rpm

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Table 14 - Physical & Chemical Stability of Prototype 11

Prototype 11	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Yellow Solution	N/A	N/A	98.3
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Yellow Solution	N/A	N/A	98.3
t = 1 mo	Conforms	N/A	N/A	98.0
t = 3 mo	Conforms	N/A	N/A	N.T
Interval	25 °C Ambient Light			
t = 0 mo	Yellow Solution	N/A	N/A	98.3
t = 1 mo	Color change	N.T	N.T	15.1
Interval	25 °C dark			
t = 0 mo	Yellow Solution	N/A	N/A	98.3
t = 1 mo	Conforms	N/A	N/A	98.9
t = 3 mo	Conforms	N/A	N/A	N.T
Interval	40 °C dark			
t = 0 mo	Yellow Solution	N/A	N/A	98.3
t = 1 mo	Conforms	N/A	N/A	99.5
t = 3 mo	Conforms	N/A	N/A	N.T

N.T = Not Tested

¹Viscosity Parameters: Spindle 27, Speed 30 rpm

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Table 15 - Physical & Chemical Stability of Prototype 12

Prototype 12	Appearance	pH (neat)	Viscosity (cps) ¹	Assay by HPLC (% of LC)
Interval	Freeze / Thaw			
t = 0 mo	Yellow Solution	N/A	N/A	98.6
t = 1 mo	Conforms	N.T	N.T	N.T
Interval	5 °C dark			
t = 0 mo	Yellow Solution	N/A	N/A	98.6
t = 1 mo	Conforms	N/A	N/A	99.0
t = 3 mo	Conforms	N/A	N/A	N.T
Interval	25 °C Ambient Light			
t = 0 mo	Yellow Solution	N/A	N/A	98.6
t = 1 mo	Color change	N.T	N.T	10.6
Interval	25 °C dark			
t = 0 mo	Yellow Solution	N/A	N/A	98.6
t = 1 mo	Conforms	N/A	N/A	98.7
t = 3 mo	Conforms	N/A	N/A	N.T
Interval	40 °C dark			
t = 0 mo	Yellow Solution	N/A	N/A	98.6
t = 1 mo	Conforms	N/A	N/A	98.3
t = 3 mo	Conforms	N/A	N/A	N.T

N.T = Not Tested

¹Viscosity Parameters: Spindle 21, Speed 60 rpm

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All the compositions presented in Table 3 showed a discoloration and/or a deterioration of the system when stored unprotected at ambient light conditions. These results indicate that the photodegradation of menadione may have a deleterious effect of unknown mechanism on the physical properties of the lotion. For this reason a container-closure system that affords 100% light protection was selected.

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EXAMPLE 3 - *In Vitro* Percutaneous Absorption of (¹⁴C)-Menadione Study #1

Simultaneously with the stability evaluation of the prototypes presented in Table 3, a second set of prototypes was prepared and evaluated for their ability to deliver menadione into the viable epidermal and dermal layers. Menadione in Dimethyl Sulfoxide (DMSO) was run as a positive control as it is well known to be an optimal skin penetration enhancer.

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The samples were initially prepared at 0.1% (w/w) Menadione and subsequently spiked with 0.1% (w/w) (¹⁴C)-Menadione to achieve tested 0.2% (w/w) concentration of

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Menadione. The study was conducted using excised human skin from a single donor obtained following elective surgery using Bronaugh Flow-Thru diffusion cells.

Skin samples were exposed to the prototype sample for 24 hours. Following exposure of the skin samples to the formulations, the degree of penetration was

- 5 measured as radioactivity in the tape-strip, epidermis, dermis and receptor fluid samples, using liquid scintillation analyzing techniques.

The composition of the evaluated prototype samples and results of their respective skin permeation values are presented in Table 16.

10 **Table 16 Composition and Percutaneous Absorption of Menadione Prototypes**

Ingredients	% w/w									
	1	2	3	4	5	13	6	8	11	14
Menadione, USP	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
(¹⁴ C)-Menadione	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Diethyl Sebacate	3.0	----	----	----	----	----	10.0	10.0	15.0	----
Diisopropyl Adipate	----	6.0	----	----	----	----	----	----	----	----
Isopropyl Myristate, NF	----	----	12.0	12.0	12.0	12.0	----	----	50.0	----
White Petrolatum, USP	----	----	----	----	----	5.0	5.0	5.0	----	----
Light Mineral Oil, NF	----	----	----	----	----	----	----	----	34.8	----
Brij 72	----	----	----	----	----	----	3.5	----	----	----
Brij 721	----	----	----	----	----	----	1.5	----	----	----
Emulsifying Wax	----	----	----	----	----	----	----	12.0	----	----
Pemulen TR-1, NF	0.3	0.3	0.3	0.3	0.3	0.3	----	----	----	----
Carbopol 981, NF	0.1	0.1	0.1	0.1	0.1	0.1	0.1	----	----	----
Methylparaben, NF	0.17	0.17	0.17	----	----	----	----	0.17	----	----
Propylparaben, NF	0.03	0.03	0.03	----	----	----	----	0.03	----	----
Benzyl Alcohol, NF	----	----	----	1.0	1.0	1.0	1.0	----	----	----
Propylene Glycol, USP	----	----	----	----	5.0	20.0	----	----	----	----
Dimethyl Sulfoxide	----	----	----	----	----	----	----	----	----	99.8
4% NaOH Solution	q.s. pH ~5.0-6.0							----	----	----
Phosphate Buffer	----	----	----	----	----	----	----	q.s. pH ~ 5.0- 6.0	----	----
Purified Water	q.s. ad 100							----		----
Average Percutaneous Absorption in Values of Percent of Applied Dose, N=5										
Tape Strips	7.2	4.9	6.7	11.2	7.4	3.9	37.5	36.3	20.6	4.36
Epidermis	30.1	33.0	35.7	40.6	32.9	32.9	25.1	25.6	31.3	36.4
Dermis	11.1	12.7	14.2	18.9	13.6	10.4	9.13	9.12	14.2	17.0
Receptor Phase	30.0	25.6	31.4	38.1	31.3	36.3	17.3	21.9	23.4	44.3
Average Skin Deposition of Menadione (mM), N=5										
Epidermis	1.06	1.16	1.26	1.43	1.16	1.16	0.88	0.90	1.10	1.28
Dermis	0.129	0.147	0.165	0.220	0.158	0.122	0.106	0.106	0.165	0.197

The percutaneous absorption results presented in Table 16 demonstrate that all of the evaluated prototypes provide adequate permeability, as all of them delivered more than 10% of the applied dose through the skin over a period of 24 hours. The epidermal concentrations were in the range of 0.88 to 1.43 mM exceeding the original goal of an estimated delivery range between 0.1 to 0.5 mM. From this data, it was apparent that the menadione concentration in the formulation could be reduced by a factor of at least four (to 0.05%) and provide an adequate concentration of menadione in the epidermal skin layer.

All formulations evaluated demonstrated adequate permeability properties; therefore the formulation selection was based mainly on physical and chemical stability as well as the physical attributes of the target formulation(s). With reference to Table 3, the following Table 17 contains a presentation of the rationale for the selection of the lead and back-up formulations.

Table 17 - Rationale for Lead and Back-up Formulation Selection

Formulation	Disposition	Rationale
1	Back Up Formulation	After 3 months at all conditions the formulation was physically and chemically stable. The formulation also demonstrated good skin permeability properties based on the in vitro percutaneous absorption study. As the drug solvent diethyl sebacate is non-compendial this formulation was selected as the back up formulation to formulation 4. Subsequently after 6 months at 25°C and 40°C large oil droplets were observed indicating physical instability.
2	Alternate Back Up Formulation	After 3 months at all conditions the formulation was physically and chemically stable. The formulation also demonstrated good skin permeability properties based on the in vitro percutaneous absorption study. This formulation was chosen as a back up to formulation as it appeared to be slightly tacky when applied to the skin.
3	Consider for future development if appropriate	This formulation showed good chemical and physical stability at all conditions after 3 months. The formulation is similar to formulation 4 with the exception of the preservative system. Formulation 3 uses a methylparaben / propylparaben preservative system whereas formulation 1 uses a benzyl alcohol preservative system. Benzyl Alcohol was preferred as the preservative as it has a better safety profile than the parabens.

Table 17 - Rationale for Lead and Back-up Formulation Selection (cont'd)

Formulation	Disposition	Rationale
4	Lead Formulation	After 3 months the formulation was physically and chemically stable. The physical appearance of the product stored at 40°C changed from a yellowish lotion to a darker shade of yellow. Despite the color change, the sample retained its chemical integrity, as evidenced by the chemical potency remaining within acceptable limits. The formulation met all the primary objectives: a. Ethyl Alcohol-free product b. Compendial formulation components c. Vehicle composed of FDA approved excipients d. Chemically stable e. Physically stable f. Highly spreadable and cosmetically elegant g. Pharmaceutically acceptable attributes h. Preserved product In addition, formulation 4 demonstrated good skin permeability properties based on the initial in vitro percutaneous absorption study.
5	Not Selected	After 3 months at 40C a significant loss of assay was observed indicating chemical instability.
6	Not Selected	After 3 months at 40°C, phase separation was observed indicating physical instability.
7	Not Selected	After 1 month at 40°C, phase separation was observed indicating physical instability.
8	Consider for future development if appropriate	Although this formulation was physically and chemically stable at all conditions after 3 months, due to the high emulsifying wax content a significant waxy residue was left on the skin. It was also not readily spreadable which may not be suitable for application over a large body surface area.
9	Not Selected	After 1 month at 40°C, phase separation was observed indicating physical instability.
10	Not Selected	After 1 month at 40°C, phase separation was observed indicating physical instability.
11	Consider for future development if appropriate	Although this formulation was physically and chemically stable at all conditions after 3 months, the formulation was significantly oily and greasy when applied to the skin. It was decided that this physical attribute was not optimal.
12	Consider for future development if appropriate	Although this formulation was physically and chemically stable at all conditions after 3 months, the formulation was significantly oily and greasy when applied to the skin. It was decided that this physical attribute was not optimal.

Based on the rationale provided in Table 17, formulation 1 and formulation 4 were carried forward for an additional in vitro percutaneous absorption study in addition to a primary packaging compatibility study.

EXAMPLE 4 - *In Vitro* Percutaneous Absorption of (¹⁴C)-Menadione Study #2

The purpose of this second *in vitro* study was to characterize the *in vitro* percutaneous absorption of (¹⁴C)-Menadione at concentrations of 0.05, 0.1, and 0.2%.

These studies were conducted with lead formulation 4 and the backup formulation 1 following topical application to dermatomed, normal human skin obtained following elective surgery.

Percutaneous absorption of (^{14}C)-Menadione was also evaluated using abraded human skin in the lead formulation at 0.05, 0.1, and 0.2% Menadione and the backup formulation at 0.2% Menadione. Abraded skin was evaluated as a possible simulation of the type of broken and/or compromised skin that may be present in the case of a skin rash caused by an EGFR inhibitor. The respective skin permeation values are presented in: Table 18.

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Table 18 – Percutaneous Absorption of Menadione

Formul.	% w/w									
	-1 (0.05%) N ¹	-1 (0.1%) N ¹	-1 (0.2%) N ¹	-1 (0.2%) A ²	-4 (0.05%) N ¹	-4 (0.1%) N ¹	-4 (0.2%) N ¹	-4 (0.05%) A ²	-4 (0.1%) A ²	-4 (0.2%) A ²
Average Percutaneous Absorption in Values of Percent of Applied Dose, N=5										
Tape Strips	8.87	6.24	5.21	7.05	4.71	5.97	5.19	4.01	2.49	3.20
Epidermis	33.4	32.7	29.8	13.4	35.8	28.6	25.2	27.6	20.3	18.6
Dermis	7.35	10.1	12.3	14.1	13.8	13.4	12.6	17.4	13.1	13.8
Receptor Phase	19.6	22.7	28.2	47.0	16.7	19.1	24.3	28.2	39.1	37.6
Average Skin Deposition of Menadione (mM), N=5										
Epidermis	0.29	0.58	1.05	0.47	0.32	0.50	0.89	0.24	0.36	0.66
Dermis	0.017	0.046	0.113	0.129	0.032	0.062	0.116	0.040	0.060	0.126

¹ N notates normal skin

² A notates abraded skin

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In summary, efficiency of (^{14}C)-Menadione skin permeation increased with increasing concentration of API in the formulations. There was no significant difference in the efficiency of (^{14}C)-Menadione skin permeation observed with Formulation 1 compared to Formulation 4 at comparable concentration of menadione and skin condition (normal or abraded). Little difference was noted in epidermal levels of menadione between the two formulations at comparable concentration of menadione. The epidermal levels of the drug were observed to be lower when applied to abraded skin. However, this observation is probably of little clinical significance since measured epidermal levels are typically associated with compound presence in stratum corneum, and also because the abrasion increased the overall penetration of menadione to the receptor, which indicates more menadione passed into and through the epidermis in the case of abraded skin. Abrading the skin prior to application of the test formulations

significantly increased (^{14}C)-Menadione skin permeation efficiency, suggesting greater delivery of menadione (and potential clinical activity) when applied to damaged skin.

5 **EXAMPLE 5 - Primary Packaging Stability Study**

A primary packaging stability study was evaluated using a new batch of the lead formulation 4 at 0.2% and 0.1% menadione for 12 months, and the back up formulation 1 at 0.2% menadione for 3 months, respectively. These two formulations were filled into aluminum tubes selected as the packaging component, with a 30 g capacity, equipped with a blind end, end sealant and a white high density polyethylene (HDPE) piercing cap. The tubes have a PE-1090-21 internal lacquer coating, and are supplied by Montebello (Part no.: 0/7/8/S/L-DO9005-SP60).

The packaged products were placed in 5°C, 25°C, and 40°C storage, protected from light and a second experiment at ambient conditions allowed exposure to ambient room light. The physical and chemical stability of the lead and back up formulation prototypes at each condition are presented in Table 19 to Table 21.

Table 19 - Physical and Chemical Stability of the Lead Menadione Topical Lotion, 0.2% in Aluminum Tubes

Formulation 4 (Lead)	Appearance	pH (neat)	Viscosity (cps) ¹	Assay by HPLC (% of LC)
Interval	5°C / dark			
t = 0 mo	Light yellow lotion	5.4	4,650	96.7
t = 1 mo	Not evaluated			98.4
t = 3 mo	Light yellow lotion	5.3	4,390	97.2
t = 6 mo	Light yellow lotion	5.2	4,870	97.7
t = 12 mo	Light yellow lotion	5.2	4,800	100.4
Interval	25°C / dark			
t = 0 mo	Light yellow lotion	5.4	4,650	96.7
t = 1 mo	Light yellow lotion	5.3	4,340	96.8
t = 3 mo	Light yellow lotion	5.4	4,230	96.9
t = 6 mo	Light yellow lotion	5.3	4,440	97.1
t = 12 mo	Light yellow lotion	5.3	4,340	100.2
Interval	Ambient Temperature / Ambient Light			
t = 0 mo	Light yellow lotion	5.4	4,650	96.7
t = 1 mo	Light yellow lotion	5.3	4,370	98.0
t = 3 mo	Light yellow lotion	5.4	4,230	98.1
t = 6 mo	Light yellow lotion	5.2	4,610	97.5

t = 12 mo	Light yellow lotion	5.3	4,520	101.4
Interval	30°C / dark			
t = 0 mo	Light yellow lotion	5.4	4,650	96.7
t = 3 mo	Slight deepening in yellow color	5.4	4,230	97.1
t = 6 mo	Slight deepening in yellow color	5.2	3,880	97.1
t = 12 mo	Slight deepening in yellow color	5.3	2,980	100.6
Interval	40°C / dark			
t = 0 mo	Light yellow lotion	5.4	4,650	96.7
t = 1 mo	Light yellow lotion	5.3	3,960	97.7
t = 3 mo	Slight deepening in yellow color	5.3	3,130	96.2
t = 6 mo	Deepening in yellow color	5.3	2,520	95.6

¹Viscosity Parameters: Spindle 27, Speed 30 rpm

Table 20 Physical and Chemical Stability of the Lead Menadione Topical Lotion, 0.1 % in Aluminum Tubes

Formulation 4 (Lead)	Appearance	pH (neat)	Viscosity (cps)¹	Assay by HPLC (% of LC)
Interval	5°C / dark			
t = 0 mo	Light yellow lotion	5.3	5,090	98.8
t = 1 mo	Not evaluated			99.4
t = 3 mo	Light yellow lotion	5.3	4,780	98.2
t = 6 mo	Light yellow lotion	5.3	5,200	96.7
t = 12 mo	Light yellow lotion	5.4	5,240	99.1 ²
Interval	25°C / dark			
t = 0 mo	Light yellow lotion	5.3	5,090	98.8
t = 1 mo	Light yellow lotion	5.3	4,780	98.6
t = 3 mo	Light yellow lotion	5.3	4,580	98.5
t = 6 mo	Light yellow lotion	5.3	4,900	96.5
t = 12 mo	Light yellow lotion	5.3	4,500	99.7
Interval	Ambient Temperature / Ambient Light			
t = 0 mo	Light yellow lotion	5.3	5,090	98.8
t = 1 mo	Light yellow lotion	5.3	4,800	101.4
t = 3 mo	Light yellow lotion	5.3	4,630	99.2
t = 6 mo	Light yellow lotion	5.3	4,980	98.5
t = 12 mo	Light yellow lotion	5.4	4,800	100.1
Interval	30°C / dark			
t = 0 mo	Light yellow lotion	5.3	5,090	98.8
t = 3 mo	Slight deepening in yellow color	5.2	4,280	99.2
t = 6 mo	Slight deepening in yellow color	5.3	4,320	96.5
t = 12 mo	Slight deepening in yellow color	5.4	3,630	98.5
Interval	40°C / dark			
t = 0 mo	Light yellow lotion	5.3	5,090	98.8
t = 1 mo	Light yellow lotion	5.3	4,420	99.7
t = 3 mo	Slight deepening in yellow color	5.2	3,600	98.0
t = 6 mo	Deepening in yellow color	5.3	3,700	94.8

¹ Viscosity Parameters: Spindle 27, Speed 30 rpm

Table 21 - Physical and Chemical Stability of the Back-Up Menadione Topical Lotion, 0.2% in Aluminum Tubes

Formulation 1 (Back-Up)	Appearance	pH (neat)	Viscosity (cps) ¹	Assay by HPLC (% of LC)
Interval	5 °C / dark			
t = 0 mo	Yellow lotion	5.4	4,060	97.1
t = 1 mo	Not evaluated			97.7
t = 3 mo	Conforms	5.4	3,930	97.1
Interval	25 °C / dark			
t = 0 mo	Yellow lotion	5.4	4,060	97.1
t = 1 mo	Conforms	5.4	3,860	97.7
t = 3 mo	Conforms	5.4	3,730	98.8
Interval	Ambient Temperature / Ambient Light			
t = 0 mo	Yellow lotion	5.4	4,060	97.1
t = 1 mo	Conforms	5.4	3,890	95.6
t = 3 mo	Conforms	5.4	3,700	99.6
Interval	40 °C / dark			
t = 0 mo	Yellow lotion	5.4	4,060	97.1
t = 1 mo	Conforms	5.4	3,590	96.8
t = 3 mo	Slight deepening in color	5.3	2,480	94.3

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¹Viscosity Parameters: Spindle 27, Speed 30 rpm

As shown in Table 19 and Table 20, the lead formulation remained physically and chemically stable under all conditions evaluated. Throughout the evaluation, parameters such as appearance, pH, viscosity and potency remained within the acceptable limits. Under the 40°C condition a deepening in color and a reduction in viscosity was observed over time.

As shown in Table 21, the back-up formulation remained physically and chemically stable under all conditions evaluated. Throughout the evaluation, parameters such as appearance, pH, viscosity and potency remained within the acceptable limits. Under the 40°C condition a deepening in color and a reduction in viscosity was observed over time.

For both the lead and back up formulations it can be seen that after 12 months at ambient condition exposed to ambient room light there was no significant change in the chemical or physical properties. This indicates that the primary packaging system provides 100% protection of the product from light and was therefore selected for the packaging of the non-clinical and clinical batches.

EXAMPLE 6 - Clinical Formula Composition

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Based on the adequate permeability of formulation 4 from both *in vitro* percutaneous absorption studies and its respective physico-chemical stability in borosilicate glass and in the primary packaging study, the compositions listed in Table 22 were selected for non-clinical and clinical evaluations.

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Table 22 - Clinical Formula Composition

Ingredients	% w/w	% w/w	% w/w
Menadione, USP	0.2	0.1	0.05
Isopropyl Myristate, NF	12.0	12.0	12.0
Pemulen TR-1, NF	0.3	0.3	0.3
Carbopol 981, NF	0.1	0.1	0.1
Benzyl Alcohol, NF	1.0	1.0	1.0
Sodium Hydroxide, NF	0.08 ¹	0.08 ¹	0.08 ¹
Purified Water, USP	86.32 ¹	86.42 ¹	86.47 ¹

¹ Estimated Quantity

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All excipients used in Menadione Topical Lotion are of the USP or NF grade. All ingredients are also listed in and are within acceptable ranges per FDA's Inactive Ingredient Guide (IIG) for topical products. The comparison of excipients to IIG acceptance limits are listed in Table 23.

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Table 23 - Comparison of Excipients to IIG Acceptance Limits

Ingredient	% w/w	Maximum Use Levels (IIG)
Isopropyl Myristate, NF	12.0	35 %
Benzyl Alcohol, NF	1.0	50 %
Pemulen TR-1, NF	0.3	1.5 %
Carbopol 981, NF	0.1	0.85 %
Sodium Hydroxide, NF	0.06	10 %

The function of each excipient is listed in Table 24.

Table 24 - Function of Excipients Used in Menadione Topical Lotion

Ingredient	Grade	Use
Isopropyl Myristate	NF	Solvent / Emollient
Benzyl Alcohol	NF	Preservative
Carbopol 981	NF	Gelling Agent
Pemulen TR-1	NF	Emulsifier / Gelling Agent
Sodium Hydroxide	NF	Neutralizer
Purified Water	USP	Carrier

Carbopol 981 conforms to the Carbomer 941, NF monograph. Pemulen TR-1
5 conforms to the Carbomer Copolymer and to the Carbomer 1342 NF monographs. Both polymers are benzene free. The FDA's Inactive Ingredient Guide refers to these materials as Carbomer 981 and Carbomer 1342, respectively.

Placebo Formulation for Menadione Lotion

10 Since the active component, menadione, is a yellow powder, and since Menadione Topical Lotion therefore has a light yellow appearance due to the menadione component, a known amount (7 ppm) of FD&C yellow #5 is dissolved in the water phase to maintain an appearance comparable to that of the drug product. The remaining ingredients in the formulation are the same as those described in Example 7. A stability
15 study was initiated to evaluate the physical and chemical stability of the Placebo for Menadione Lotion formulation. The Placebo for Menadione Lotion formulation was compounded in borosilicate clear glass vials. All vials were stored at 5°C (dark), 25°C (dark) and 40°C (dark) to assess the stability of the placebo formulation. The physical and chemical stability results are provided in Table 25.

20

Table 25 - Physical and Chemical Stability of Placebo for Menadione Lotion

Lot 2560-13A	Appearance	pH (neat)	Viscosity (cps) ¹
Interval	5 °C / dark		
t = 0 mo	Yellow lotion	N.T	N.T
t = 3 mo	Yellow lotion	5.1	4,700
t = 6 mo	Yellow lotion	5.2	4,700
Interval	25 °C / dark		
t = 0 mo	Yellow lotion	N.T	N.T
t = 3 mo	Yellow lotion	5.1	4,400
t = 6 mo	Yellow lotion	5.2	4,300
Interval	40 °C / dark		
t = 0 mo	Yellow lotion	N.T	N.T
t = 3 mo	Yellow lotion	5.2	3,800
t = 6 mo	Yellow lotion	5.2	3,700

N.T = Not Tested

¹Viscosity Parameters: Spindle 21, Speed 60 rpm

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EXAMPLE 7 – Batch Formulations for Use in Clinical Studies

Three 37.5 Kg clinical Menadione Topical Lotion batches were manufactured at concentrations of 0.2%, 0.1% and 0.05%. The clinical supplies were packaged in 60g aluminum tubes with blind end, end sealant and a black polypropylene (PP) piercing cap. The tubes have a PE-1090-21 internal lacquer coating, and are supplied by Montebello (Part no.: 1/1/4/S/L-HA1020-SP22). During development, the cap color was changed from white to black because it was surprisingly discovered that use of white caps allowed light penetration into the product after breaking the seal, resulting in product deterioration in the area around the neck of the tube that received the minimal light exposure. This is in accordance with stability observations as noted in Table 7, for example.

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15

The respective batch formulas are provided in Table 26 to Table 28.

Table 26 Menadione Topical Lotion, 0.2% Batch Formula

Ingredients	Quality Standard	% w/w	Batch Quantity (g)³
Menadione	USP	0.20	75.0
Isopropyl Myristate	NF	12.00	4,500.0
Benzyl Alcohol	NF	1.00	375.0
Pemulen TR-1	NF	0.30	112.5
Carbopol 981	NF	0.10	37.5
Sodium Hydroxide	NF	<u>0.08^{1,2}</u>	30.0 ^{1,2}
Purified Water	USP	<u>86.32¹</u>	32,370.0 ¹

¹ Estimated Quantity² Sodium Hydroxide solution added to q.s. pH 5.5 – 6.0³ Quantity per batch for a 37.5 Kg Batch

5

Table 27 Menadione Topical Lotion, 0.1% Batch Formula

Ingredients	Quality Standard	% w/w	Batch Quantity (g)³
Menadione	USP	0.10	37.5
Isopropyl Myristate	NF	12.00	4,500.0
Benzyl Alcohol	NF	1.00	375.0
Pemulen TR-1	NF	0.30	112.5
Carbopol 981	NF	0.10	37.5
Sodium Hydroxide	NF	<u>0.08^{1,2}</u>	30.0 ^{1,2}
Purified Water	USP	<u>86.42¹</u>	32,407.5 ¹

¹ Estimated Quantity² Sodium Hydroxide solution added to q.s. pH 5.5 – 6.0³ Quantity per batch for a 37.5 Kg Batch

10

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Table 28 Menadione Topical Lotion, 0.05% Batch Formula

Ingredients	Quality Standard	% w/w	Batch Quantity (g)³
Menadione	USP	0.05	18.75
Isopropyl Myristate	NF	12.00	4,500.00
Benzyl Alcohol	NF	1.00	375.00
Pemulen TR-1	NF	0.30	112.50
Carbopol 981	NF	0.10	37.50
Sodium Hydroxide	NF	0.08 ^{1,2}	30.00 ^{1,2}
Purified Water	USP	86.47 ¹	32,426.25 ¹

¹ Estimated Quantity² Sodium Hydroxide solution added to q.s. pH 5.5 – 6.0³ Quantity per batch for a 37.5 Kg Batch

5

Placebo Lotion for Menadione

Additionally, one 37.5 Kg clinical Placebo batch was manufactured. The batch
 10 formula is provided in Table 29.

Table 29 Placebo Lotion for Menadione Batch Formula

Ingredients	Quality Standard	% w/w	Batch Quantity (g)³
Isopropyl Myristate, NF	USP	12.00	4,500.00
Benzyl Alcohol, NF	NF	1.00	375.00
FD&C Yellow #5	Supplier Standard	0.0007	0.26
Pemulen TR-1, NF	NF	0.30	112.50
Carbopol 981, NF	NF	0.10	37.50
Sodium Hydroxide, USP	NF	0.08 ^{1,2}	30.00 ^{1,2}
Purified Water, USP	USP	86.5193 ¹	32444.74 ¹

¹ Estimated Quantity² Sodium Hydroxide solution added to q.s. pH 5.5 – 6.0³ Quantity per batch for a 37.5 Kg Batch

15

EXAMPLE 8 – Clinical Formulations

Menadione Topical Lotion, containing concentrations of 0.05%, 0.1%, or 0.2% (w/w), can be used for treatment of rash secondary to epidermal growth factor receptor inhibitor (EGFRI) therapies and other skin conditions. The product is essentially a yellow to light yellow lotion with target pH of 5.5 to 6.0 and a viscosity of approximately 3,000 to 4,000 cps using the following viscosity parameters, Spindle 27, Speed 30 rpm. The formulation is specifically designed to facilitate complete dissolution of menadione drug substance in the oil-phase and to maintain its overall solubility of either 0.05%, 0.1% or 0.2% menadione (w/w) in the lotion formulation.

Manufacturing Process Development

The manufacturing process for Menadione Topical Lotion, 0.05%, 0.1%, or 0.2%, is conducted under yellow light to prevent the degradation of the active pharmaceutical ingredient (API) as it is known to be photosensitive, and subsequently the deterioration of the finished product.

The compounding process is typical of commercial scale manufacturing of emulsions. The oil phase and aqueous phase are prepared separately, heated to 70°C, and are then combined with high shear mixing to form an emulsion. Upon cooling, the emulsion is additionally thickened by raising the pH to a range of 5.5 -6.0 by the addition of a 2% sodium hydroxide solution to produce a homogeneous product.

Container Closure System

Information on the container closure is provided below in Table 29.

Table 29 Container Closure System

Container	Dimensions	Material / Internal Coating	Crimp Sealant	Manufacturer	Part Number	Use
60-g capacity, white aluminum tube with blind end, and a black polypropylene (PP) piercing cap	Body Length with cap: 5.25 inches Tube outer diameter: 1.25 inches	1170 Alloy / PE-1090-21 internal lacquer coating	Darex CMPD AD 2311B LS	Montebello Packaging 1036 Aberdeen St. Hawkesbury, Ontario K6A 1K5 Canada	1/1/4/S/L-HA1020-SP22	Clinical batches

5 Microbiological Attributes

Based on formulation development experience using benzyl alcohol as a preservative in topical formulations, benzyl alcohol was selected as the preservative system in the menadione formulations. Subsequent anti-microbial effectiveness testing (AET) has demonstrated the effectiveness of the preservative system in the selected lead formulation. The Menadione Topical Lotion, 0.2% passed the USP and EP/BP requirements of the AET test. Acceptable AET results for the 0.2% formulation means that the same formulations containing less menadione (for example, 0.05% and 0.1%) are also acceptable.

15 Compatibility

An LDPE applicator commercially available for delivery of various similar products will be used to facilitate accurate clinical dosing. The expected contact time between the candidate drug product and the applicator is not expected to exceed 5 minutes.

20

EXAMPLE 9 – Characterization of Menadione Topical Lotion for the Prevention and Treatment of Skin Toxicities Associated with EGFR Inhibitor Therapy

Background: Acneform rash is a pervasive, painful, and treatment-limiting complication of EGFR inhibitor therapy with reported incidence rates ranging from 50-100%.

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Menadione Topical Lotion (MTL) is being developed as a targeted treatment for this side effect of EGFR inhibitors, of which there are 4 approved agents (erlotinib, gefitinib, panitumumab and cetuximab). Menadione has been shown to have direct EGF activating activity as well as EGFR and other growth factor-related phosphatase inhibitory activity.

5

Methods: This Phase 1, placebo-controlled, open-label, modified dose-escalation study assessed the bioavailability, safety and tolerability of three concentrations (0.05%, 0.1%, 0.2%) of MTL and placebo administered BID on face, neck, upper chest and upper arms of subjects for 3.5 days in a 7 day cycle over a 28 day period. The pharmacokinetic parameters of MTL were assessed in blood and tissue and the major metabolites menaquinone-4 and thiodione were assessed in blood. Potential response biomarkers p27, p63 and pEGFR, were measured in skin.

Results: Twelve normal subjects, 6 male and 6 female, with a median age of 43 years (range, 30-52) were entered into the study. Plasma drug levels were analyzed and negligible plasma menadione concentrations near the lower limit of quantification were observed in a small sample of patients. This confirms that topical menadione has no significant systemic absorption. The most frequent adverse events (AEs) potentially related to MTL included skin toxicities of erythema and a burning sensation. All AEs were CTC Grade 1 or 2. Immunohistochemical analysis of p27, p63 and pEGFR suggest that normal skin structure and signaling was not adversely affected by MTL.

Conclusions: Pharmacokinetic analysis of plasma from MTL treated subjects demonstrated insignificant systemic levels of menadione and its major metabolites menaquinone-4 and thiodione. MTL is being developed for EGFR inhibitor therapy-associated skin toxicity (rash) and is currently under investigation in a Phase 1 study in cancer patients receiving EGFR inhibitor therapy.

EQUIVALENTS

Throughout this specification the disclosures of various publications, the full citations of which were referred to in parenthesis, are hereby incorporated by reference in their entireties into the subject application to more fully describe the art to which the subject application pertains.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

5

What is claimed is:

1. A topically applicable pharmaceutical formulation suitable for treatment of a dermatological condition comprising a vitamin K analog, a lipophylic component, a
10 gelling agent, and water.
2. The pharmaceutical formulation of claim 1, wherein the vitamin K analog activates EGFR.
- 15 3. The pharmaceutical formulation of claim 2, wherein the vitamin K analog is menadione.
4. The pharmaceutical formulation of claim 1, comprising from about 0.01 to 10% (w/w) of the vitamin K analog.
20
5. The pharmaceutical formulation of claim 1, wherein the lipophilic component is selected from the group consisting of isopropyl myristate, caprylic/capric triglyceride, diethyl sebacate, diisopropyl adipate, petrolatum, mineral oil, and cyclomethicone.
25
6. The pharmaceutical formulation of claim 1, comprising from about 1 to 100% (w/w) of the lipophilic component.
7. The pharmaceutical formulation of claim 1, comprising from about 0.1 to
30 5% (w/w) of the gelling agent.
8. The pharmaceutical formulation of claim 1, comprising from about 30 to 95% (w/w) water.

9. The pharmaceutical formulation of claim 1, further comprising a preservative.

5 10. The pharmaceutical formulation of claim 9, comprising from about 0.01 to 50% (w/w) of the preservative.

11. The pharmaceutical formulation of claim 1, further comprising a neutralizing agent.

10

12. The pharmaceutical formulation of claim 11, wherein the neutralizing agent maintains the pH of the formulation at about 4.0 to 8.0.

13. The pharmaceutical formulation of claim 1, wherein the formulation is a
15 cream or a lotion.

14. The pharmaceutical formulation of claim 13, wherein the formulation is a lotion with a viscosity of approximately 1,000 to 20,000 cps.

20 15. A topically applicable pharmaceutical formulation suitable for treatment of a dermatological condition comprising,

- a) from about 0.01 to 10% (w/w) of menadione;
- b) from about 1 to 50% (w/w) of a lipophilic component;
- c) from about 0.01 to 5% (w/w) each of one or more acrylic acid based polymers;
- 25 e) from about 0.03 to 10% (w/w) of a preservative;
- f) a neutralizing agent sufficient to maintain a pH of about 4.0 to 7.0; and
- g) water.

16. The pharmaceutical formulation of claim 15 comprising,
30 a) from about 0.05 to 2% (w/w) of menadione;
b) from about 3 to 20% (w/w) of the lipophilic component;
c) from about 0.1 to 1.0% (w/w) each of one or more acrylic acid based polymers;

- e) from about 0.5 to 5% (w/w) of the preservative;
- f) a neutralizing agent sufficient to maintain a pH of about 4.5 to 6.5; and
- g) purified water.

- 5 17. The pharmaceutical formulation of claim 15, comprising
- a) about 0.05 to 0.2% (w/w) menadione;
 - b) about 12% (w/w) isopropyl myristate;
 - c) about 0.3% (w/w) Pemulen TR-1;
 - d) about 0.1% (w/w) Carbopol 981;
 - 10 e) about 1% (w/w) benzyl alcohol;
 - f) sodium hydroxide sufficient to maintain a pH of about 5.0 to 6.0; and
 - g) purified water.

- 15 18. The pharmaceutical formulation of claim 15, comprising
- a) about 0.05 to 0.2% (w/w) menadione;
 - b) about 3% (w/w) diethyl sebacate;
 - c) about 0.3% (w/w) Pemulen TR-1;
 - d) about 0.1% (w/w) Carbopol 981;
 - e) about 0.3% (w/w) each of methylparaben and propylparaben;
 - 20 f) sodium hydroxide sufficient to maintain a pH of about 5.0 to 6.0; and
 - g) water.

- 25 19. The pharmaceutical formulation of claim 15, comprising
- a) about 0.05 to 0.2% (w/w) menadione;
 - b) about 6% (w/w) diisopropyl adipate;
 - c) about 0.3% (w/w) Pemulen TR-1;
 - d) about 0.1% (w/w) Carbopol 981;
 - e) about 0.3% (w/w) each of methylparaben and propylparaben;
 - f) sodium hydroxide sufficient to maintain a pH of about 5.0 to 6.0; and
 - 30 g) water.

20. A packaged pharmaceutical formulation comprising the pharmaceutical formulation of claim 1 or 15 packaged in a light impermeable container.

21. A method of treating a dermatological condition comprising topically administering to a patient a therapeutically effective amount of the pharmaceutical formulation of claim 1 or 15 or the packaged pharmaceutical formulation of claim 20.

5

22. The method of claim 21, wherein the dermatological condition is secondary to an anti-epidermal growth factor receptor (EGFR) therapy.

23. The method of claim 22, wherein the anti-EGFR therapy is treatment
10 with an anti- EGFR antibody.

24. The method of claim 22, wherein the anti-EGFR therapy is treatment with an EGFR tyrosine kinase inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/037041

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/107 A61K31/122 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/058398 A1 (KAMEI YUTO [JP] ET AL) 16 March 2006 (2006-03-16) paragraph [0029] example 9	1-24
X	----- DATABASE WPI Week 200555 Thomson Scientific, London, GB; AN 2005-537568 XP002531129 & JP 2005 206521 A (NIPPON MENARD KESHOHIN KK) 4 August 2005 (2005-08-04) abstract examples 1,3,4,6	1-24
X	----- EP 0 392 845 A (MINNESOTA MINING & MFG [US]) 17 October 1990 (1990-10-17) page 6, line 13 claims 8,9 ----- -/-	1-24

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *G* document member of the same patent family

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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International application No

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