



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US96/09545 (22) International Filing Date: 5 June 1996 (05.06.96) (30) Priority Data: 08/469,474 6 June 1995 (06.06.95) US (71) Applicant (for all designated States except US): NEUTROGENA CORPORATION [US/US]; 5760 West 96th Street, Los Angeles, CA 90045 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MATHER, Kamran [US/US]; 29679 Quail Run Drive, Agoura Hills, CA 91301 (US). STAHL, Christopher, Ryan [US/US]; 5400 West 123rd Street, Hawthorne, CA 90250 (US). (74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson &amp; Johnson, One Johnson &amp; Johnson Plaza, New Brunswick, NJ 08933-7003 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p>
<p>(54) Title: TOPICAL VEHICLES CONTAINING SOLUBILIZED AND STABILIZED AZELAIC ACID</p>		
<p>(57) Abstract</p> <p>A completely solubilized topical composition of azelaic acid in a glycol base which is stable at normal temperatures and pressures and which is useful as a commercial substitute for dispersed azelaic acid preparations.</p>		

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TOPICAL VEHICLES CONTAINING SOLUBILIZED  
AND STABILIZED AZELAIC ACID

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## INTRODUCTION

The present invention relates to topical compositions containing azelaic acid and glycol and more particularly to new and improved compositions containing stabilized and completely solubilized azelaic acid.

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## BACKGROUND OF THE INVENTION

This invention relates to a completely solubilized and stable topical formulation of azelaic acid at normal temperatures and standard atmospheric pressures. Topical azelaic acid formulations have been used to address a wide range of physiological maladies including acne, hyperpigmentary dermatoses, hair loss, wrinkling, hyperhidrosis, non-acne inflammatory dermatoses, infectious cutaneous diseases and ichthyosis.

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However, the only topical formulations of azelaic acid presently known are dispersions. Dispersions deliver azelaic acid in an undissolved state. When applied to the skin, undissolved azelaic acid is not readily absorbed and as a result an excess of azelaic acid must be present to be effective. The higher the concentration of azelaic acid, the more likely irritation (burning, stinging and redness) to the skin will occur.

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What is needed is a completely solubilized topical azelaic acid composition. Solubilized azelaic acid is much less likely to irritate the skin because azelaic acid in a dissolved state is much more readily absorbed by the

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need be present in the formulation to be effective thereby lowering the risk of irritation to the skin.

5 While azelaic acid is somewhat soluble in water, cosmetic oils and alcohols, each of these solvents has serious limitations. Thus, water only marginally dissolves azelaic acid so that a water and azelaic acid solution would contain a maximum of about .24% by weight (w/w) azelaic acid, not likely enough to be effective.  
10 Azelaic acid has little or no solubility in cosmetic oils. Alcohols are good solvents but are unsatisfactory because large amounts of alcohol e.g., isopropyl alcohol, in a topical composition has the undesirable side effect of drying the skin. Indeed, some alcohols e.g., ethyl  
15 alcohol, render azelaic acid unstable at normal temperatures and atmospheric pressures resulting in a totally ineffective composition.

20 U.S. Patent Nos. 4,292,326 (Nazzaro-Porro, Sep. 29, 1981), 4,386,104 (Nazzaro-Porro, May 31, 1983), and 4,818,768 (Nazzaro-porro, Apr. 4, 1989) all teach dispersions of non-solubilized azelaic acid containing 10% - 20% (w/w) azelaic acid.

25 U.S. Patent Nos. 4,713,394 (Thornfeldt, Dec. 15, 1987) and 4,885,282 (Thornfeldt, Dec. 5, 1989) both teach two formulations, A and B, of azelaic acid. Formulation A is an azelaic acid formulation containing a large proportion of ethanol. While ethyl alcohol dissolves  
30 azelaic acid, it also renders the azelaic acid unstable at normal temperatures and atmospheric pressures meaning a marketable product is not possible. Formulation B teaches a dispersion of azelaic acid.

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Japan Patent No. 59,020,213 (Shiseido) teaches a hair cosmetic emulsion containing no azelaic acid but a chemical derivative of azelaic acid. The derivative is not completely solubilized but only partially dissolved in a water-glycol base.

A emulsion containing 10 - 20% concentration of azelaic acid in a base of water, apple pectin and sunflower oil was taught by Berova, N., et al. in "Hypoallergic Cosmetic Emulsion with Azelaic Acid for Prophylaxy and Treatment of Acne Vulgaris," Berova, N., Nkiolova, A., Kratchanov, Chr., and Popova, M., Journal of Applied Cosmetology, vol. 12, no. 3, p. 51 (1994). Berova et al. attribute the mildness of their formulation to the use of natural ingredients like apple pectin and sunflower oil instead of non-natural substances in the azelaic acid vehicle. The emulsion taught by Berova et al. is not completely solubilized and suffers from the same problem as do the Nazzaro-Porro and Thornfeldt formulations, the weight percent of azelaic acid in the formulation is higher than needed because the azelaic acid is not completely solubilized.

The art has yet to find a formulation for completely solubilizing azelaic acid at normal temperatures and atmospheric pressures without sacrificing the stability of the solubilized azelaic acid. Solubilized azelaic acid must remain stable at normal temperatures and atmospheric pressures in order to provide a marketable product.

Without a stable, completely solubilized formula of azelaic acid, the benefits of azelaic acid are unavailable to many users who experience the burning, stinging and redness of the skin associated with exposure to high

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levels of undissolved azelaic acid in dispersions. The present invention provides a completely solubilized and stable formulation of azelaic acid in a glycol base at normal temperatures and pressures and whose shelf life makes a marketable product possible and reduces the amount of azelaic acid the user must be exposed to in order to enjoy its benefits.

## BRIEF SUMMARY OF THE INVENTION

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This invention relates to topical compositions of azelaic acid and more specifically to compositions containing stabilized and completely solubilized azelaic acid and glycol that are used to treat a wide variety of skin conditions. The present invention delivers azelaic acid to the skin in a completely solubilized yet stable form thus insuring excellent absorption by the skin and significantly reducing the incidence of skin irritation.

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Azelaic acid, a straight chain dicarboxylic acid with 9 carbons, has limited solubility in water and commonly used cosmetic oils. Low levels of azelaic acid (from about 0.5% (w/w) to about 10% (w/w)) may be completely dissolved in glycol (from about 20% (w/w) to about 60% (w/w)) and remain in stable solution. The glycol utilized may be one or more of the following: propylene glycol, polypropylene glycol, dipropylene glycol, butylene glycol, polyethylene glycol, methoxypolyethylene glycol, ethoxydiglycol, polypropylene glycol ethers, and hexylene glycol, although other glycols that readily dissolve azelaic acid may also be selected.

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Accordingly, a primary object of the invention is to provide a stable and completely solubilized formulation containing azelaic acid.

5 Another object is to provide lower, yet effective, concentrations of a topical azelaic acid formulation that is less likely to irritate the skin of the user.

10 A further object of the invention is to provide a stable, solubilized azelaic acid formulation that can be stored for long periods at normal temperatures and atmospheric pressures.

15 A still further object is to provide a completely solubilized and stabilized topical formulation containing azelaic acid that addresses a large variety of skin conditions.

20 These and still further objects as shall hereinafter appear are fulfilled by the present invention in a remarkably unexpected fashion as will be readily discerned from a careful consideration of the following detailed description of preferred embodiments thereof especially when read in conjunction with the several examples  
25 appended thereto.

#### DESCRIPTION OF THE PREFERRED EMBODIMENT

30 The present invention relates to a topical cosmetic preparation containing azelaic acid stabilized and completely solubilized in a glycol base. The preparation is used to treat a wide variety of skin ailments with little or no irritation to the skin. The glycol easily and completely dissolves the azelaic acid without

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affecting the stability of the azelaic acid. The absence of ethanol or other destabilizing solvents insures the azelaic acid remains stable.

5           The glycol utilized may be one or more of the following: propylene glycol, polypropylene glycol, polypropylene glycol ethers, hexylene glycol, dipropylene glycol, butylene glycol, polyethylene glycol, methoxypolyethylene glycol and ethoxydiglycol, although  
10 other glycols that readily dissolve azelaic acid may also be selected. The amount of glycol may vary from about 20% to 60% (w/w). 20% (w/w) glycol is the minimum amount required to solubilize an effective amount of azelaic acid. 60% (w/w) is probably the maximum level that could  
15 be used without completely sacrificing the formulation's aesthetics. Somewhere in the middle of this range is most ideal.

          Preferably, a cream or gel topical solution can be  
20 made with about 1 - 10% (w/w) of azelaic acid dissolved in about 20 - 60% (w/w) glycol. If lower levels (about 0.5 to about 2.5% (w/w)) of azelaic acid are used, the glycol level can be reduced and conventional emulsions with cosmetic oils formed. With levels of glycol greater than  
25 30% (w/w), emulsion stability is sacrificed. But with glycol levels of about 20% to about 30% (w/w) the stability of emulsions with moisturizing ingredients are acceptable. Moreover, the addition of moisturizing ingredients greatly improve the aesthetics of creams and  
30 gels.

To further aid in the understanding of the present invention, and not by way of limitation, the following examples are presented:



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## EXAMPLE 1

In one practice of the present invention, and our preferred embodiment thereof, a topical cream is produced by mixing about 20.0 to 60.0% (w/w) of ethoxydiglycol, about 3% (w/w) of diisopropyl adipate and about 1.0 % to 10.0% (w/w) of azelaic acid until a clear solution is formed. In a separate container, q.s. distilled water and about 5.0% (w/w) of PEG-60 almond glycerides are mixed and heated to 70°C. To this mixture, about 8% (w/w) of glycol distearate is added and all three ingredients are mixed while maintaining a temperature of 70°C until the whole forms a white homogeneous fluid. This mixture was allowed to cool to 40°C to which the azelaic acid-ethoxydiglycol-diisopropyl adipate mixture is added. About 2.5% (w/w) of a mixture of polyacrylamide, C13-C14 isoparaffin and Laureth 7, (which mixture is available as SEPIGEL 305 from Seppic Department Cosmetique-Pharacie, Paris, France), is then added and the whole was mixed until a thick and homogeneous cream resulted.

A translucent gel can be made from the above formulation by removing the glycol distearate therefrom.

## EXAMPLE 2

In another preferred practice of the present invention, a topical cream is produced by mixing about 1.0% to 10.0% (w/w) of azelaic acid with about 20.0% to 60.0% (w/w) of dipropylene glycol and heating the mixture to about 60°C until a clear solution is formed. The solution is then cooled to and maintained at 40°C. In a separate container, about 5.0% (w/w) PEG-60 almond glycerides and q.s. distilled water are mixed and heated

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to about 70°C. To this mixture, about 8.0% (w/w) of glycol distearate is added and all three ingredients are mixed while maintaining a temperature of 70°C until the whole forms a white homogeneous fluid. This mixture is then allowed to cool to 40°C and the azelaic acid-dipropylene glycol mixture is added thereto and mixed therein. About 2.0% (w/w) of a mixture of polyacrylamide, C13-C14 isoparaffin and Laureth 7 (SEPIGEL 305) is then added and the whole mixed until a thick and homogeneous cream results.

A translucent gel can be made from the above formulation by removing the glycol distearate therefrom.

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## EXAMPLE 3

In yet another practice of the present invention, an emulsion with commonly used cosmetic oils is made by mixing about 0.5% to 2.5% (w/w) of azelaic acid with about 20.0% to 30.0% (w/w) of dipropylene glycol and q.s. distilled water which mixture is then heated to 70°C until a clear solution results. In a separate container, about 10.0% (w/w) of C12-C15 Alkyl benzoate, about 3.0% (w/w) of isododecane, about 6.0% (w/w) of cyclomethicone, about 2.5% (w/w) of stearyl alcohol, about 4.0% (w/w) of a commercial mixture of glyceryl stearate and PEG-100 stearate, (available as ARLACEL 165 from ICI American Inc., Wilmington, Delaware), and about 0.1% (w/w) of a commercial mixture of isopropylparaben, isobutylparaben and butylparaben, (available as LIQUAPAR OIL from Sutton Laboratories, Chatham, N.J.), were mixed and heated to about 70°C. To this mixture the azelaic acid-dipropylene glycol-water mixture (also at 70°C) is added and the whole mixed while maintaining the temperature at 70°C. The

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mixture is then allowed to cool to 45°C. Lastly, about 0.8% (w/w) of SEPIGEL 305 is added and the whole mixed until thick and homogeneous.

5           Each of the products produced by the foregoing Examples, hereinafter designated "Formula 1", "Formula 2" and "Formula 3", respectively (each Formula number corresponding to the Example by which it was produced, was then tested following the methods outlined in: Grove,  
10 G.L., Soschin, A.M. and Kligman, A.M., "Guidelines for Performing Facial Stinging Tests," available from Skin Study Center, Simon Greenburg Foundation, 3901 Market Street, Philadelphia, PA and the Duhring Laboratories, Department of Dermatology, University of Pennsylvania  
15 School of Medicine, Philadelphia, PA 19104, and incorporated herein by this reference thereto.

The effectiveness of Formula 1 was tested on a panel of 17 individuals having reddish or hyperpigmented skin.  
20 The discoloration of the skin was measured using a MINOLTA CHROMAMETER Model CR-200. The panelists applied Formula 1 to the discolored skin once per day for 4 weeks. At the end of the 4 week period the skin discoloration was again measured using the MINOLTA CHROMAMETER. Results showed a  
25 significant reduction of skin discoloration for the group as an average.

The mildness of Formulae 2 and 3 were tested on a panel of 18 people, some of whom were classified as  
30 "stingers." A "stinger" is a person who experiences stinging, burning or itching after an application of 5% lactic acid solution to the naso-labial area of the face. These "stingers" are considered to have sensitive skin.

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Results of the tests showed that both formulas were considered to be mild using Kligman's scale.

5 From the foregoing, it is apparent that novel and  
unique topical vehicles containing solubilized and  
stabilized azelaic acid have been herein described and  
illustrated which fulfills all of the aforestated  
objectives in a remarkably unexpected fashion. It is, of  
course understood that such modifications, variations or  
10 adaptations as may readily occur to an artisan familiar  
with the art to which this invention pertains are intended  
within the spirit of this invention which is limited only  
by the scope of the claims appended hereto.

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## CLAIMS

Accordingly what is claimed is:

- 5           1. A topical composition comprising azelaic acid completely solubilized in a glycol wherein said solubilized azelaic acid is stable at normal temperatures and standard atmospheric pressures.
- 10           2. The composition according to claim 1 wherein said glycol is selected from the group consisting of propylene glycol, polypropylene glycol, dipropylene glycol, butylene glycol, polyethylene glycol, methoxy polyethylene glycol, polypropylene glycol ethers, hexylene glycol, and  
15           ethoxydiglycol.
3. The composition according to claim 1 comprising from about 0.5% to about 10% (w/w) of said azelaic acid.
- 20           4. The composition according to claim 3 comprising from about 20.0% to about 60.0% (w/w) of said glycol.
5. The composition according to claim 4 wherein said glycol is selected from the group consisting of propylene  
25           glycol, polypropylene glycol, dipropylene glycol, butylene glycol, polyethylene glycol, methoxy polyethylene glycol, polypropylene glycol ethers, hexylene glycol, and ethoxydiglycol.
- 30           6. The composition according to claim 1 comprising from about 0.5% to about 2.5% (w/w) of said azelaic acid.
7. The composition according to claim 6 comprising from about 20% to about 30% (w/w) of said glycol.

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8. The composition according to claim 7 wherein said glycol is selected from the group consisting of propylene glycol, polypropylene glycol, dipropylene glycol, butylene glycol, polyethylene glycol, methoxy polyethylene glycol, polypropylene glycol ethers, hexylene glycol, and ethoxydiglycol.

9. The composition according to claim 6 further comprising about 20.0% to about 30% (w/w) of dipropylene glycol, about 10.0% (w/w) of C12-15 alkyl benzoate, about 3.0% (w/w) of isododecane, about 6.0% (w/w) of cyclomethicone, about 2.5% (w/w) of stearyl alcohol, about 4.0% (w/w) of a mixture of glyceryl stearate and PEG-stearate, about 0.1% (w/w) of a mixture of isopropyl paraben, isobutyl paraben and butyl paraben, about 0.8% (w/w) of a mixture of polyacrylamide, C13-C14 isoparaffin and Laureth 7 and q.s. distilled water.

10. The composition according to claim 1 comprising from about 1% to about 10 % (w/w) of said azelaic acid.

11. The composition according to claim 10 comprising about 20.0% to about 60% (w/w) of said glycol.

12. The composition according to claim 11 wherein said glycol is selected from the group consisting of propylene glycol, polypropylene glycol, dipropylene glycol, butylene glycol, polyethylene glycol, methoxy polyethylene glycol, polypropylene glycol ethers, hexylene glycol, and ethoxydiglycol.

13. The composition according to claim 10 further comprising about 20% to about 60% ethoxydiglycol, about 3.0% (w/w) of diisopropyl adipate, about 5.0% (w/w) of

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PEG-60 almond glycerides, about 8.0% (w/w) of glycol distearate, about 2.5% (w/w) of a mixture of polyacrylamide, C13-C14 isoparaffin and Laureth 7 and q.s. distilled water.

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14. The composition according to claim 10 further comprising about 20 % to about 60% (w/w) dipropylene glycol, about 5.0% (w/w) of PEG-60 almond glycerides, about 8.0% (w/w) of glycol distearate, about 2.0% (w/w) of a mixture of polyacrylamide, C13-C14 isoparaffin and Laureth 7 and q.s. distilled water.

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# INTERNATIONAL SEARCH REPORT

Int. Patent Application No  
PCT/US 96/09545

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K7/48

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)  
IPC 6 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)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Week 8411 Derwent Publications Ltd., London, GB; AN 84-065028 XP002011083 "Oil-in-water emulsion for hair cosmetics - comprises water-sol. solvent, polyalkylene glycol polyether or polyalkylene glycol satd. acid ester and water" &amp; JP,A,59 020 213 (SHISEIDO) , 1 February 1984 cited in the application see abstract</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

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**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/US 96/09545

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>JOURNAL OF APPLIED COSMETOLOGY, vol. 12, no. 3, 1994, pages 51-55, XP000579273 N. BEROVA ET AL: "Hippoallergic cosmetic emulsion with azelaic acid for prophylaxy and treatment of Acne bulgaris" cited in the application see page 53; claim 1 ---</p>	1
A	<p>EP,A,0 229 654 (THORNFELDT) 22 July 1987 cited in the application see claim 1; example 1 ---</p>	1
A	<p>GB,A,2 283 421 (PROCTER &amp; GAMBLE) 10 May 1995 see claims 1,2 ---</p>	1
A	<p>WO,A,95 04537 (PROCTER &amp; GAMBLE) 16 February 1995 see page 22; claims 1,5; example VII ---</p>	1
P,A	<p>WO,A,95 24179 (PROCTER &amp; GAMBLE) 14 September 1995 see claim 1 -----</p>	1

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 96/09545

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		JP-A- 7309751	28-11-95
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