DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR - 7 2000

TRANSMITTED VIA FACSIMILE

Ronald G. Van Valen
Associate Director
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

RE: **NDA 50-737, 50-738**
Neoral (cyclosporine capsules for microemulsion) Soft Gelatin Capsules
Neoral (cyclosporine oral solution for microemulsion) Oral Solution
MACMIS#: 8498

Dear Mr. Van Valen:

As part of our routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials for Neoral Soft Gelatin Capsules and Neoral Oral Solution by Novartis Pharmaceuticals Corporation that violate the Federal Food, Drug and Cosmetic Act (Act) and its implementing regulations. Reference is made to promotional materials NPS-0001, NPS-1003-A, NPS-1004, CNPS-1004, CNPS-1006, NPS-2006, NPS-2007, NPS-2008, NPS-2009, NPS-2010, NPS-2011 B,C, NPS-2012, NPS-2014, NPS-2017, NPS-8016, CNEO-1114, NPS-8008 and NPS-9102.

**False and Misleading Claims**

*Efficacy*

You are making false and misleading claims in your materials by presenting higher efficacy rates for Neoral compared to the efficacy rates found in the pivotal studies. You claim that 87% of patients achieve remission by week 16. However, the percentages for achieving remission in the pivotal studies are 51.1%, 79.1% and 80.6% for 8, 16 and 24 weeks respectively in the efficacy

population, and 49%, 80.2% and 82.9% for 8, 16, and 24 weeks respectively in the intent-to-treat population. Therefore, as stated in our March 3, 1998, launch comments to you, this claim is false or misleading because it suggests that Neoral is more effective than has been demonstrated.

*Rotation with other therapies*

In your promotional materials (including NEO-2046, CNPS-1004 and NPS-8008), you make the claim that Neoral can be rotated with other therapies to limit the side effects associated with the long-term use of a single drug. This claim implies it is an option to alternate, but does not communicate that continuous treatment is NOT recommended. This claim is misleading because it is not consistent the information from the prescribing information that states, *Long term experience with Neoral in psoriasis patients is limited and continuous treatment for extended periods greater than one year is not recommended. Alternation with other forms of treatment should be considered in long term management of patients with this life long disease.*

**Unsubstantiated Claims**

Several of your materials present statements that comment on the negative psychosocial impact of psoriasis. For example, *For many patients, the chief disability isn't physical its psychological* and *Psoriasis has been linked to low self-esteem, depression, obesity, increased alcohol consumption and suicide.* These claims in the context of promotion of Neoral, are false or misleading because they imply that Neoral has an effect on psychosocial functioning that has not been demonstrated.

In your promotional material NPS 2014-A, you list under the heading titled, *Quality of Life Issues:*

- *Decreased ability to work and/or manage a home*
- *Restricted recreational activities*
- *Limited personal and/or social relationships*
- *Physically painful and/or emotionally disabling*

These claims, in the context of promotion of Neoral, are misleading because they imply that Neoral has an effect on physical, mental and social functioning that has not been demonstrated by substantial evidence.

Furthermore, in your promotional material NPS-2007, under the heading titled, *Neoral Promotes Patient Satisfaction,* you make claims such as *I've got my life back – the Neoral difference* and *Neoral makes me feel like a normal human being.* These claims are false and misleading because they make implied and explicit claims that Neoral promotes patient satisfaction that are not supported by substantial evidence.

**Brief Summary**

*Professional journal*

According to regulations, all advertisements for any prescription drug shall present a true statement of information in brief summary relating to side effects, contraindications and effectiveness. You placed advertisements for Neoral in a "wrap-around" fashion in the May 1999 issue of SKIN & AGING (CNPS-1004) and also the September 1999 issue of THE LANCET (CNEO-1114). These presentations are two separate and distinct advertisements (back and front covers) and each requires an accompanying brief summary. However, the front cover advertisement is not accompanied by a brief summary. Further, the Psoriasis and Transplant brief summaries presented on the respective back panels of the journals are missing information from the ADVERSE REACTIONS and WARNINGS sections of the approved labeling.

**Lack of Risk Information**

*Visual aid*

Your promotional piece NPS-1004-A lacks fair balance or is otherwise misleading because it presents several statements that minimize the risk of developing kidney failure while taking Neoral, without presenting the serious boxed warning information about kidney failure. For example, you quote, "[A]lthough some loss of renal function occurs in many patients, it is mild, reversible, and acceptable given the benefits that derive from treatment." You however, do not present the boxed warning that states that Neoral in recommended dosages can cause nephrotoxicity. In addition, the warning section of the prescribing information states that since cyclosporine is a potent immunosuppressive agent with a number of potential side effects, the risks and benefits of using Neoral should be considered before treatment of patients with psoriasis.

Similarly, your presentation on skin malignancy and lymphoma presents statements that minimize the risk for developing these diseases without presenting the boxed warning from the prescribing information about these diseases. For example, you state that the relative risk of developing lymphoma and/or skin malignancies with cyclosporine is comparable to that observed in psoriasis patients treated with other systemic agents. However, you do not present the boxed warning that states that psoriasis patients previously treated with PUVA and to a lesser extent, methotrexate or other immunosuppressive agents, are at an increased risk of developing skin malignancies when taking Neoral.

*Note pad*

Your promotional piece NPS -2012 (note pad) is lacking in fair balance because it presents the claim, "remission accomplished" without presenting any risk information.

**Photographs**

The photographs and slides in your promotional piece NPS-8016[1] do not accurately represent severe, recalcitrant psoriasis and are therefore, are false and misleading because they suggest that Neoral is useful in a broader range of conditions than indicated.

**Action Requested**

You should immediately cease distribution of these promotional materials and all other promotional materials for Neoral that contain the same or similar claims or presentations cited in this letter. You should submit a written response to us, on or before March 21, 2000, describing your intent and plans to comply with the above. In your letter to us, you should include a list of all promotional materials that were discontinued, and the discontinuation dates.

You should direct your response to me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered

[1] Response of patient 02-005 in study OLP-452

official. In all correspondence regarding this particular submission, please refer to MACMIS ID# 8498 in addition to the NDA number.

Sincerely,

/S/

Cheryl Y. Roberts
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

NPS-2012

Remission Accomplished.

NEORAL®
(cyclosporine capsules and oral solution for microemulsion)


# It's Time to Clear the Air.

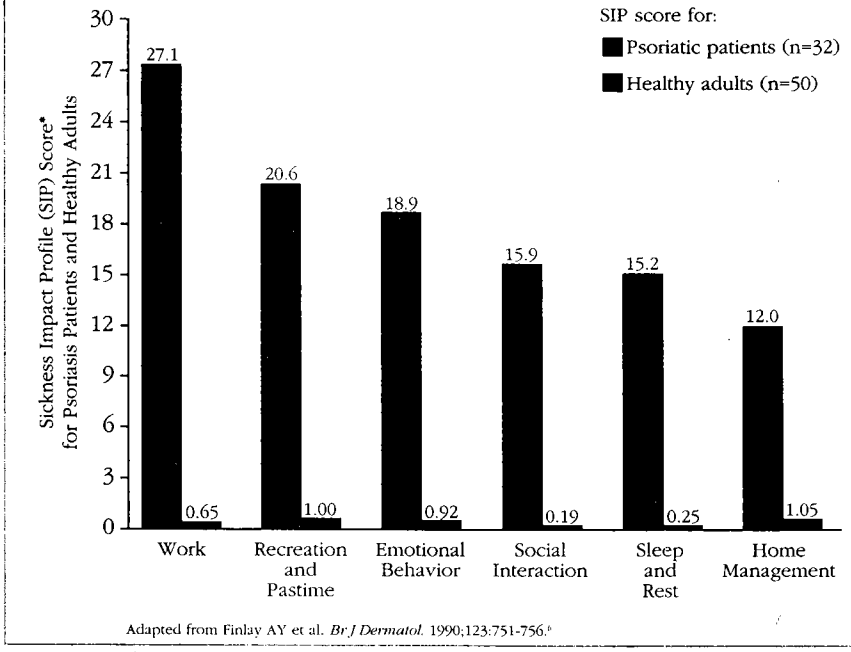
*Psoriasis itself may not kill, but its effects can be devastating. Psoriasis has been linked to low self-esteem, depression, obesity, increased alcohol consumption, and suicide. All of these reflect the impact severe psoriasis has on a patient's quality of life.[1,2] Therefore, perhaps it's time to take a new look at the extent of the psychosocial effects of this chronic condition.*

## How Do Patients *Really* Feel?

Psoriasis, by attacking the skin, attacks the very identity of an individual. Numerous studies have documented the anguish and enormous disruption people with severe psoriasis experience in their daily lives, their relationships, and in their perception of themselves.[3,4] A survey of psoriasis patients revealed that 20% lost time from work or school, 49% stopped sports or hobbies, and 28% had to limit their social lives due to their disease.[5]

Not surprisingly, many patients also report having to deal with feelings of helplessness, shame and embarrassment, guilt, anger, and frustration on a daily basis.[4] These feelings of lowered self-esteem, compounded by loss in leisure time and decreased days at work due to psoriasis, provide compelling evidence of the profound psychosocial and physical effect severe psoriasis has on a patient's quality of life.

The impact of severe psoriasis on important daily functions.




Adapted from Finlay AY et al. *Br J Dermatol.* 1990;123:751-756.[6]

**SIP is a performance-based questionnaire consisting of 136 health-related statements in 12 areas of daily activity, measuring the impact of disease on patient functional ability: 0 = no impact; 30 = high impact.*

## The Power of Partnership

What *is* surprising: Many patients feel that the devastating effect of this disease on their lives is not recognized by others, including their health care providers, which often makes treating severe psoriasis frustrating for both physicians and patients.[4]

Therefore, clinical assessment of psoriasis should include a clear understanding of the patient's perspective of disease severity and its impact on quality of life.[4,6]

Likewise, patient preference for treatment based on clinical efficacy, time to response, tolerability, and convenience are also important considerations when evaluating your therapeutic options.

Working together with your patients to establish their individual needs, hopes, and expectations will enable you to choose the most appropriate therapy, which in turn will help you to optimize outcomes.

*Remission Accomplished.*

**NEORAL®**
**(cyclosporine capsules and oral solution for microemulsion)**

**Please see accompanying prescribing information for Neoral.**

Neoral® is indicated for the treatment of adult, nonimmunocompromised patients with severe (ie, extensive and/or disabling), recalcitrant plaque psoriasis who have failed to respond to at least 1 systemic therapy (eg, PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated or cannot be tolerated.

**References:** 1. Krueger GG, Duvic M. *J Invest Dermatol.* 1994;102:14S-18S. 2. Ginsburg IH. *Dermatol Clin.* 1995;13:793-804. 3. Finlay AY, Coles EC. *Br J Dermatol.* 1995;132:236-244. 4. Koo J. *Dermatol Clin.* 1996;14:485-496. 5. McHenry PM, Doherty VR. *Br J Dermatol.* 1992;127:13-17. 6. Finlay AY, Khan GK, Luscombe DK, et al. *Br J Dermatol.* 1990;123:751-756.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

*When the effects of psoriasis are devastating...*

# Neoral® Offers Patients Rapid Relief for Real Life

- Promotes rapid clearing—improvement can be seen within 2 to 4 weeks
  - 51% and 87% of patients achieved remission by 8 and 16 weeks, respectively†
- Provides highly effective control at low doses—2.5 to 4.0 mg/kg per day
- Can be alternated with other therapies
- Offers patients important lifestyle options
- Has an acceptable safety profile* with appropriate monitoring

*For more information about Neoral, call* 1-877-4NEORAL

*The principal adverse reactions associated with the use of cyclosporine in psoriasis are renal dysfunction, headache, hypertension, hypertriglyceridemia, hirsutism/hypertrichosis, paresthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhea, abdominal discomfort, lethargy, and musculoskeletal or joint pain. Patients should be informed of the necessity for repeated laboratory tests.

Neoral is contraindicated in patients with abnormal renal function, uncontrolled hypertension, or malignancies. Psoriasis patients who are treated with Neoral should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar, or radiation therapy.

*Remission Accomplished.*

NEORAL®
(cyclosporine capsules and oral solution for microemulsion)

*Please see brief summary of Neoral prescribing information on following page.*

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936



Printed in U.S.A. 9/99 C-NPS-1006 Printed on Recycled Paper

# Are My Patients at Risk for Developing Kidney Failure?

- Vasoconstriction, the primary cause of mild elevations in serum creatinine with cyclosporine (CsA) therapy, is physiologic and rapidly reversible with dose reduction and/or discontinuation[1]
- Structural/histologic renal changes occur slowly over time and are rare at the low, recommended doses when serum creatinine levels are maintained ≤25% above baseline[1,2]
  - CsA does not cause acute renal failure
- Serum creatinine levels must be elevated by *50%* above baseline for ***over 3 months*** before the statistical risk of irreversible kidney damage begins to rise[3]
- Potentially serious renal side effects can be easily detected ***and*** avoided by monitoring serum creatinine, a clear marker of kidney function

*"[M]ost often renal dysfunction reflects only an isolated change in vascular...function. [A rise in serum creatinine is] generally fully reversible and [is]not associated with any structural damage to the kidney."*

June Mason, MD.
*Transplant Proc.* 1990.

*"[A]lthough some loss of renal function occurs in many patients, it is mild, reversible, and acceptable given the benefits that derive from treatment."*[2]

Mark Lebwohl, MD.
*J Am Acad Dermatol.* 1998.


References:

1. Mason J. Renal side-effects of cyclosporine. *Transplant Proc.* 1990;22:1280-1283.
2. Lebwohl M, Ellis C, Gottlieb A, et al. Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. *J Am Acad Dermatol.* 1998;39:464-475.
3. Data on file, Novartis Pharmaceuticals Corporation.


*Remission Accomplished.*

NEORAL®
(cyclosporine capsules and oral solution for microemulsion)

# Should I Be Concerned About Hypertension and Lymphoma?

## Hypertension (HTN)

- HTN is a common side effect, dose-dependent, and generally mild to moderate in severity
  - In pivotal clinical trials, increases in systolic BP ranged from approximately 2-6 mm Hg; increases in diastolic BP ranged from approximately 4-6 mm Hg[1-3]
- Increases in blood pressure will return to baseline levels with dose reduction/discontinuation
- HTN can be effectively controlled with dose reduction (new-onset and/or preexisting HTN) or antihypertensive agents (preexisting HTN)

## Lymphoma and Skin Malignancy

- The relative risk of developing lymphoma and/or skin malignancies with cyclosporine is comparable to that observed in psoriasis patients treated with other systemic agents[4-6]

| | % Incidence | |
|---|---|---|
| | Lymphoma | Skin Malignancy |
| Cyclosporine[4] | 0.1% | 1.1% |
| Other Systemics[5,6] (eg, PUVA, MTX) | 0.1% | 0.7%-1.4% |

MTX = methotrexate; BP = blood pressure.

*Please see enclosed complete prescribing information for Neoral®.*

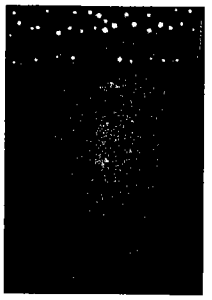
References:
1. Shupack J, Abel E, Bauer E, et al. Cyclosporine as maintenance therapy in patients with severe psoriasis. *J Am Acad Dermatol.* 1997;36:423-432.
2. Ellis CN, Fradin MS, Hamilton TA, et al. Duration of remission during maintenance cyclosporine therapy for psoriasis: relationship to maintenance dose and degree of improvement during initial therapy. *Arch Dermatol.* 1995;131:791-795.
3. Data on file, Novartis Pharmaceuticals Corporation.
4. Lamarque V, Monka C, Commare MC, et al. Risk of malignancies in patients treated with Sandimmun® for autoimmune diseases. In: Touraine JL et al, eds. *Cancer in Transplantation. Prevention and Treatment.* The Netherlands: Kluwer Academic Publishers; 1996:141-148.
5. Lindelöf B, Sigurgeirsson B, Tegner E, et al. PUVA and cancer: a large scale epidemiological study. *Lancet.* 1991;338:91-93.
6. Olsen JH, Møller H, Frentz G. Malignant tumors in patients with psoriasis. *J Am Acad Dermatol.* 1992;27:716-722.

*Remission Accomplished.*

NEORAL®
(cyclosporine capsules and oral solution for microemulsion)

Baseline

Photograph patient #2 OLP-452

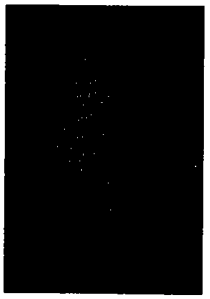


Week 2

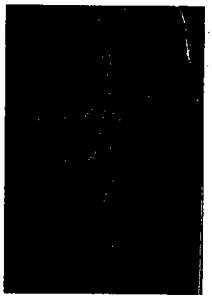
Week 4

Week 6

Week 8

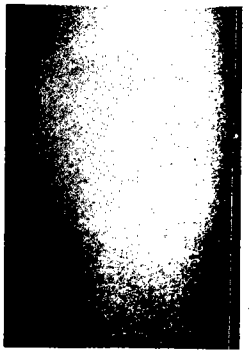


Week 10



Week 12

Data on file, Novartis Pharmaceuticals Corporation. Unretouched photographs of psoriatic lesions document response of patient 02-005 in Study OLP-452.



Week 16

*Please see enclosed full prescribing information for Neoral.*

- Promotes clearing within 2 to 4 weeks
- Provides highly effective control of psoriasis at low doses—2.5 to 4.0 mg/kg per day
- Can be rotated with other therapies
- Offers patients important lifestyle options
- Has an acceptable safety profile with appropriate patient monitoring

---

Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine, and, therefore, renal function must be monitored during therapy.

*Remission Accomplished.*

NEORAL®
(cyclosporine capsules and oral solution for microemulsion)

# NEORAL® PROMOTES PATIENT SATISFACTION

## "I'VE GOT MY LIFE BACK."
The Neoral Difference

"I wear shorts now."
Chris Bernard, Charleston, SC

"My skin feels normal again, more relaxed, more elastic."
Earnest Carillo, Detroit, MI

"I'm not afraid to be seen anymore."
Deborah Ganson, Portland, OR

"My wife is so happy with the improvement."
Peter Levkowicz, Austin, TX

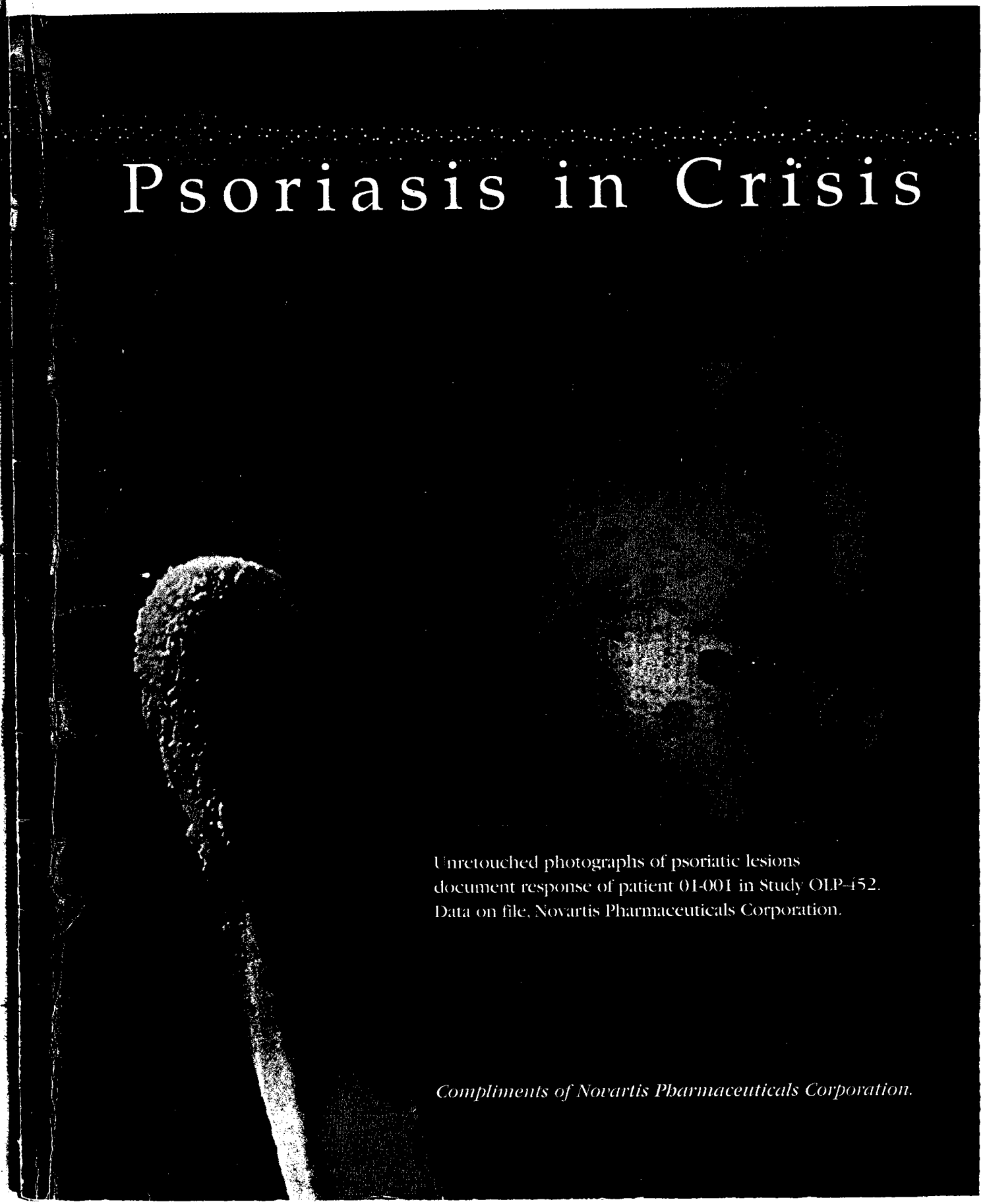
"Neoral makes me feel like a normal human being."
Mary Williams, Albany, NY

Neoral is indicated for the treatment of adult, nonimmunocompromised patients with severe (ie, extensive and/or disabling), recalcitrant plaque psoriasis who have failed to respond to at least one systemic therapy (eg, PUVA, retinoids, or methotrexate), or in patients for whom other systemic therapies are contraindicated or cannot be tolerated. Psoriasis patients who are treated with Neoral should not receive concomitant PUVA or UVB therapy, methotrexate, or other immunosuppressive agents, coal tar, or radiation therapy. Neoral is contraindicated in psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies. Neoral has increased bioavailability as compared to Sandimmune® (cyclosporine, USP). Neoral and Sandimmune are not bioequivalent and cannot be used interchangeably without physician supervision.

NEORAL®
(cyclosporine capsules and oral solution for microemulsion)

# *Skin & Aging*

## Psoriasis in Crisis



Unretouched photographs of psoriatic lesions document response of patient 01-001 in Study OLP-152. Data on file, Novartis Pharmaceuticals Corporation.

*Compliments of Novartis Pharmaceuticals Corporation.*

# Remission Accomplished.

- Baseline PASI score: 35
- Neoral® dose: 2.5 mg/kg per day for 16 weeks
- Time to remission: 8 weeks*†

Baseline Week 4 Week 8 Week 12

*Remission was defined as ≥75% improvement in scaling, erythema, and thickness of lesions as measured by PASI (Psoriasis Area and Severity Index) score.

†Results of a dose-titration clinical trial with Neoral indicate that improvement of psoriasis by >75% (based on PASI) was achieved in 51% and 79% of patients after 8 and 12 weeks, respectively.

Neoral is indicated for the treatment of adult, nonimmunocompromised patients with severe (ie, extensive and/or disabling), recalcitrant plaque psoriasis who have failed to respond to at least 1 systemic therapy (eg, PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated or cannot be tolerated.

Only physicians experienced in the management of systemic immunosuppressive therapy for the treatment of psoriasis should prescribe Neoral.

Neoral is contraindicated in patients with abnormal renal function, uncontrolled hypertension, or malignancies. Psoriasis patients who are treated with Neoral should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar, or radiation therapy.

*Remission Accomplished.*

NEORAL®
(cyclosporine capsules and oral solution for microemulsion)

*Please see brief summary of Neoral prescribing information on inside back cover of cover wrap.*

# Neoral® Offers Patients Rapid Relief for Real Life

- Promotes rapid clearing—improvement can be seen within 2 to 4 weeks
- Provides highly effective control of psoriasis at low doses—2.5 to 4.0 mg/kg per day
- Can be rotated with other therapies to limit the side effects associated with the long-term use of a single drug
- Offers patients important lifestyle options—convenient twice-daily oral dosing and no need for organ biopsy
- Has an acceptable safety profile with appropriate monitoring

The principal adverse reactions associated with the use of cyclosporine in psoriasis are renal dysfunction, headache, hypertension, hypertriglyceridemia, hirsutism/hypertrichosis, paresthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhea, abdominal discomfort, lethargy, and musculoskeletal or joint pain. Patients should be informed of the necessity for repeated laboratory tests.

Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine, and, therefore, renal function must be monitored during therapy. Psoriasis patients previously treated with PUVA and, to a lesser extent, methotrexate or other immunosuppressive agents, UVB, coal tar, or radiation therapy are at an increased risk for developing skin malignancies when taking Neoral.

*Please see brief summary of Neoral prescribing information on inside back cover of cover wrap.*

*Remission Accomplished.*

**NEORAL®**
**(cyclosporine capsules and oral solution for microemulsion)**

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936



Printed in U.S.A. 4/99 CNPS-1004