**RESEARCH CONSENT FORM**

**Protocol Title:** A randomised, controlled comparative study of the wrinkle reduction benefits of a No-Tox®, a plukenetia/niacinamide/plankton-based topical cosmeceutical formulation vs. 0.5 mg (0.05% w/w) tretinoin, a prescription-strength topical retinoic acid formulation

(**Abbreviated Name: No-tox Vs. Retinoid Study: NOVRET Study**)

**Principal Investigator:** Allanah Knight

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**Sponsor:** Skin Surgery Clinic, 271A Blockhouse Bay Road, Auckland 0600

This document consists of 5 pages (with Appendices 13 pages with last page blank for notes regarding any additional participant queries)

This is a research study, and participation is completely voluntary. You can ask questions at any time. No children or someone unable to provide consent themselves will be part of this study.

**PURPOSE OF STUDY**

* We are studying whether a cosmeceutical (skincare) product such as No-Tox can have a comparable clinical efficacy in wrinkle-reduction to that of prescription topical therapies such as retinoids (Tretinoin). Both products have, in previous studies, shown benefits in reducing wrinkles.
* Approximately 60 people will take part in this study, divided into two equal groups, chosen at random.

**PROCEDURE OF THE STUDY**

* Before you participate in the study, you will have a skin exam and the study process will be clearly explained to you. You must feel free to ask any questions.
* Randomisation means that you are put into a group by chance, like flipping a coin. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in either group.
* You will be at the Skin Surgery Clinic where your face will be scanned using a facial 3D scanner (Pear 3-D model). The scanner works by bouncing light from different light sources across your face and measuring sun damage and wrinkles. There is no radiation, or x-rays involved. This measurement will be done at 1 month and 3 months after using the study products during the course of the study.
* At the end of the study we will review these images and measure wrinkle depth. These allow researchers within our team to assess if the treatments showed any benefit, and the comparable benefits, if any, in the two treatment groups.
* We will collect information about your skin health just like we regularly do. However, some of the information collected will be used for research purposes. Specific information that will be used for research purposes includes clinical images i.e. facial scans mentioned earlier. Protected health information will include details such as name, date of birth, medical record number, and demographic information (age, sex, ethnic group), related to you and your participation in this study.

**WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?**

* No additional responsibilities are necessary to take part in the research.

**POTENTIAL BENEFITS**

* Your skin may benefit by showing less wrinkling.
* Patients assigned to one group may benefit to a greater degree than in the other group.
* You will receive free skin products for the duration of the study at no cost to you. Both study products have shown benefits in reducing wrinkles in previous studies.

**POTENTIAL RISKS/DISCOMFORTS:**

* Potential risks of participating in this study include breach of confidentiality and privacy. Loss of confidentiality will be minimised by storing data in a secure location and in password-protected, and encrypted cloud servers.
* You may develop a skin or allergic reaction to a product. In this case you will receive treatment and you will be removed from the study. Redness and peeling are some of the known side effects of retinoids that make up one arm of this study.
* If you were injured in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

**ALTERNATIVES TO PARTICIPATION**

* Your alternative is to not take part in this study. If you choose not to take part, your healthcare at the Skin Surgery Clinic will not be affected in any way. You will remain a valued client.

**COSTS TO PARTICIPANTS**

* It will not cost you anything to take part in this study
* The Skin Surgery Clinic will incur all costs related to this research, including purchasing the study skin products for your use.
* Participants in this study will not incur any additional costs.

**PAYMENT TO PARTICIPANTS**

* Participants will not be paid for participation in this study
* Medical staff will be on hand to treat any research related allergies or skin reactions that can occur with the use of any skincare products.
* There will be no compensation for research related skin reaction. If you are unable to tolerate a product, you will be removed from the study.
* The researchers conducting this study will not receive any payment for this research from the manufacturers of the study products.

**CONFIDENTIALITY AND ACCESS TO RECORDS**

* This study will involve accessing confidential information in the participant’s medical record such as scanned images. This information will be de-identified and kept on password-protected computers.
* Only the study investigators will have access to this information. You, the participant will be issued a random number.
* We cannot promise complete security and secrecy given the nature of computer systems, even when all precautions are taken.
* A description of this clinical trial will be available on ANZCTR (Australia and New Zealand Clinical Trials Registry). This Web site will not include information that can identify you. At most, the Web site will include a summary of the results.
* The data from the study may be published. By participating in this study, you are granting permission to the use of your images in a research paper. However, you will not be identified by name.

**RIGHT TO WITHDRAW**

* Your participation in this study is voluntary. You do not have to take part in this research.
* You are free to withdraw your consent at any time. If you decide to withdraw early, there is no risk, side effects or discomfort.
* Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits. If you do withdraw, you will not receive study skin products for your use.

**CAN I BE REMOVED FROM THE RESEARCH?**

* The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include failure to follow instructions of the research staff or if the person in charge decides that the research study is no longer in your best interest such as if you developed a skin allergy or reaction.
* The sponsor can also end the research study early. The study doctor will tell you about this and the reasons if this was to occur.

**STATEMENT CONCERNING RESEARCH RISKS**

* The products being used for this study are used routinely for wrinkle reduction either as a cosmetic or prescription creams and are already available commercially over-the-counter or via prescription.
* The study products are manufactured to full GMP standards, at FDA-licensed or equivalent standards.
* The Medsafe safety data sheet for Tretinoin is attached and will be discussed at the initial meeting. You are requested to read the document and ask questions prior to signing this form.
* The research described in this consent form has been classified as minimal risk by the research team and associated university.

**HAS AN ETHICS APPROVAL COMMITTEE APPROVED THIS STUDY?**

This study will be approved by an independent group of people called a Health and Disability Ethics Committee (HDEC), who check that studies meet established ethical standards prior to this being presented to participants.

**WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?**

If you have any questions, concerns, or complaints about the study at any stage, you can contact:

Ms Allanah Knight, RN and Manager

Skin Surgery Clinic Phone: 09 8286438 Option 1

Email: doctor@skinsurgeryclinic.co.nz

If you want to talk to someone who isn’t involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050

Fax: 0800 2 SUPPORT (0800 2787 7678)

Email: advocacy@advocacy.org.nz

Website: https://www.advocacy.org.nz/

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4ETHIC

Email: hdecs@health.govt.nz

**SIGNING THIS FORM**

Signing this consent form indicates that you have read this consent form and that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form. If you agree to participate in this study, please sign your name below.

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Participant’s Signature

Date:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Investigator or Designee Obtaining Consent Signature

Date:

**Appendix 1: No-Tox full ingredient list**

Water/Aqua/Eau

Glycerin

Niacinamide

Sodium Hyaluronate

Hydrolyzed Plukenetia Volubilis Seed Extract

Panthenol

Disodium EDTA

Methylglucoside Phosphate

Copper Lysinate/Prolinate

Lecithin

Ruttnera Lamellosa Oil

Watanabea Reniformis Oil

Sodium ascorbate

Tocopherol

Sodium Citrate

Ethylhexylglycerin

Phenoxyethanol

Citric Acid

\*Incidentals: Sodium Benzoate

**Manufactured under license by Smoothe Inc, USA at Neutraderm, FDA-license as below:**

**Neutraderm Inc.**

**20660 Nordhoff Street**

**Chatsworth, CA 91311**

**LICENSE NUMBER: 49515**

**EXPIRATION DATE: 6/24/2022**

**Food and Drug Branch, CA, USA**

**Appendix 2: Tretinoin MedSafe data safety sheet**

# PRODUCT NAME

ReTrieve Cream

# QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains 0.5 mg (0.05% w/w) tretinoin Excipients with known effect:

Methyl hydroxybenzoate Propyl hydroxybenzoate

For a full list of excipients see section 6.1.

# PHARMACEUTICAL FORM

Topical cream

ReTrieve is a smooth, pale yellow cream.

# CLINICAL PARTICULARS

* 1. Therapeutic indications

ReTrieve Cream is indicated for topical application in the treatment of acne vulgaris, primary grades I-III in which comedones, papules and pustules predominate. It is not recommended as mono- therapy in cases of severe pustular and deep cystic nodular varieties (acne conglobata).

Adjunctive treatment of dry skin due to chronic exposure to sunlight and related conditions

* 1. Dose and method of administration

Dosage

ReTrieve should be applied sparingly to the affected areas once daily at bedtime.

Procedural steps critical to the safe administration of the medicine Begin the treatment program slowly.

* + 1. Wash the affected areas with mild soap-free cleansers prior to any application. Pat dry.
    2. First night apply, leave for five minutes; then wash off.
    3. Second night apply, leave for ten minutes; then wash off.
    4. Third, fourth, fifth and sixth nights, increase the treatment time each night by 30 minutes until the application is left on for two hours.
    5. If after a two-hour application, no redness or irritation has developed on the skin the following day, then the application may be left on overnight and washed off next morning.
    6. If excessive skin reactions occur, adjust the schedule to alternate nights until the skin accommodates.

Advice for monitoring

Treatment with tretinoin should be individualised according to tolerance and response. No other topical preparations should be applied over the nightly inunction, but suitable moisturisers may be used during the day.

Certain types of skin could be too sensitive to ReTrieve. Patients with very sensitive skin should consult a dermatologist before commencing treatment.

* 1. Contraindications

Hypersensitivity to tretinoin or any of the ingredients in the formulation (see section 6.1).

* 1. Special warnings and precautions for use

Do not swallow and avoid contact with mucous membranes or open wounds. ReTrieve should not be applied to the eyes, mouth, lips, mucosa, or angles of the nose. Should any of these occur, rinse the affected areas thoroughly with water to avoid local irritation.

Over enthusiastic use or too frequent application may cause redness, stinging and discomfort. If severe irritation occurs, especially at the early stage of therapy, patient should be advised to discontinue temporarily or reduce the frequency of application.

Eczema

Particular caution is indicated for patients with eczema, since tretinoin has been reported to cause severe irritation on eczematous skin. The hands should be washed thoroughly with water after each application.

Concomitant application of topical preparations

Concomitant application of other topical preparations including cosmetics should be avoided if possible during the nightly inunction, because of possible incompatibility and interaction with tretinoin. Particular caution should be exercised in the use of keratolytic agents such as sulphur, salicylic acid, benzoyl peroxide or resorcinol and chemical abrasives. If the patient has been treated with such preparations, the effect of the peeling agents must subside before any commencement of topical ReTrieve therapy.

Some medicated cleansers and scrubbing solutions have a strong drying effect. They should not be used in patients receiving tretinoin topical therapy.

Exposure to Sunlight

Exposure of the treated areas to sunlight including sunlamps should be minimised during the course of topical treatment with ReTrieve. Patients receiving tretinoin treatment are more susceptible to the effect of UV irradiation especially at the start of the therapy. Animal studies suggest that tretinoin may accelerate the tumorigenic potential of ultraviolet radiation in hairless albino mice, especially at high concentrations of the drug. Although the significance to humans is unknown, patients undergoing tretinoin treatment should exercise utmost caution.

Patients with sunburn should be advised to use ReTrieve only after the skin is fully recovered. Exposure to ultraviolet irradiation increases the intensity of inflammatory reaction. Patients receiving ReTrieve therapy should avoid exposure to artificial sunlamps or solarium. Patients should be counselled to routinely use high SPF sunscreen as well as protective clothing while undergoing ReTrieve topical treatment, especially those individuals at risk of chronic sun exposure or having a family history of light sensitivity. Extreme weather conditions, such as strong wind or cold dry air may cause skin irritation to patients receiving tretinoin treatment.

* 1. Interaction with other medicines and other forms of interaction

Concomitant use of other topical medications (especially those containing keratolytic agents such as resorcinol, sulphur, salicylic acid, benzoyl peroxide and abrasive chemicals etc.) should be avoided in patients undergoing treatment with ReTrieve because of possible inter-actions with tretinoin. The application of ReTrieve should only commence after the effect of the peeling agents has completely subsided (see section 4.4).

Tretinoin is an unstable compound that is often incompatible with substances found in topical preparations. Some topical products and certain cosmetics contain high concentrations of alcohol, spices, lime, menthol. They should be used with caution especially in the early phase of treatment due to stinging action of these chemicals.

Laboratory Tests

Reversible changes in liver function tests have been reported after administration of tretinoin topical therapy but do not appear to be of clinical significance.

Elevated serum level of bilirubin, alkaline phosphatase, glutamic-pyruvic transaminase, glutamic oxaloacetic transaminase, or increase in thymol turbidity and flocculation were observed but in all cases reported, the results reverted to normal on discontinuing treatment.

* 1. Fertility, pregnancy and lactation

Pregnancy

Category D

There have been isolated reports of birth defects in babies born to women using topical tretinoin in pregnancy. To date, there have been no adequate and well controlled prospective studies in women using topical tretinoin in pregnancy. A retrospective cohort study of babies born to 215 women exposed to topical tretinoin during the first trimester of pregnancy found no more birth defects among these babies than those born to 430 women in the same cohort who were not similarly exposed.

Oral tretinoin has been shown to be teratogenic in rats when given at doses of 5 mg/kg/day and fetotoxic in rats when given at doses of 2.5 mg/kg/day. Oral doses of tretinoin have caused limb defects in mice. However, topical tretinoin has not been shown to be teratogenic in rats and rabbits when given at doses of 0.5 mg/kg/day and 1.6 mg/kg/day, respectively. These latter changes may be considered variants of normal development and are usually corrected after weaning.

In view of the possible association of tretinoin with foetal disorders, ReTrieve therapy is not recommended during pregnancy or in women of childbearing potential.

Lactation

There is insufficient information on the excretion of topical tretinoin into human milk during breast feeding. The use of ReTrieve during lactation is not recommended.

* 1. Effects on ability to drive and use machines

It is unlikely that ReTrieve will have any effects on the ability to drive and use machines.

* 1. Undesirable effects

ReTrieve is generally well tolerated after nightly application. Side effects have been limited to mild irritation, evidenced by peeling and erythema, especially in the early stage of treatment. Some patients may experience a transitory sensation of warmth or slight stinging after application of the drug.

If excessive reactions occur, the frequency of application may be reduced or treatment discontinued temporarily till the reactions subside. The dose and frequency may then be adjusted to a level which the patient can tolerate.

Temporary hyperpigmentation or hypopigmentation has occurred with repeated topical application of the drug.

Contact allergy has been reported in isolated instances.

Increased sensitivity to UV light may be experienced in patients undergoing treatment and appropriate measures should be taken (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

* 1. Overdose

No data are available on the consequences of overdosage from accidental ingestion of ReTrieve. Tretinoin is a normal metabolite of vitamin A and has similar toxicity profile. The LD50 of tretinoin in mice and rats has been found to be 4g/kg and 2g/kg respectively. The concentration of tretinoin present in ReTrieve at 0.5mg/g is unlikely to cause any symptomatic effects and any acute toxicity arising from accidental ingestion of the preparation will be more related to the toxicity of the vehicle components.

Symptoms of acute toxicity would be of gastrointestinal disturbance. In such event, treatment such as gastric lavage, inducing emesis and/or forced fluids should be performed as soon as possible.

Overdosage from excessive dermal application may produce marked erythema and skin inflammatory reactions. Should this occur, discontinue use and if necessary, apply cold compresses and/or mild emollient.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# PHARMACOLOGICAL PROPERTIES

* 1. Pharmacodynamic properties

Pharmacotherapeutic group: Retinoids for topical use in acne. ATC Code: D10AD01 Skin Protectant

The precise mechanism of action of topical tretinoin has not been fully elucidated. Tretinoin, being a metabolite of retinol, is both pharmacologically and structurally related to vitamin A which regulates

cell growth and differentiation. It has been postulated that it acts by enhancing epithelial proliferation and accelerating epithelial differentiation.

* 1. Pharmacokinetic properties

Tretinoin, an *all*-*trans* retinoic acid, occurs in the body as a tissue metabolite of vitamin A. Unlike retinol and its esters, it does not accumulate in the body but metabolises rapidly and excretes in the form of inactive glucuronides or oxidation products. These metabolites are mainly excreted in the faeces and some oxidised metabolites are found in the urine.

Topically applied tretinoin appears to be slightly absorbed from the skin. Studies in human skin showed that only a small percentage of the applied dose could be detected in urine.

# PHARMACEUTICAL PARTICULARS

* 1. List of excipients Cetyl alcohol Diazolidinyl urea Disodium edetate

DL-alpha tocopheryl acetate Glyceryl monostearate Isopropyl palmitate

Methyl hydroxybenzoate Polysorbate 60

Propyl hydroxybenzoate Propylene glycol Purified water

Retinol palmitate Sorbitan stearate

* 1. Incompatibilities

Not applicable

* 1. Shelf life

36 months

* 1. Special precautions for storage

Store below 250C.

* 1. Nature and contents of container

Tube, aluminium, polypropylene cap: 5g, 50g

* 1. Special precautions for disposal <and other handling>

No special requirements

# MEDICINE SCHEDULE

Prescription

# SPONSOR

iNova Pharmaceuticals (New Zealand) Limited c/- Simpson Grierson

88 Shortland Street,

Auckland 1141

Toll-free number: 0508 375 394

# DATE OF FIRST APPROVAL

26 November 2009

# DATE OF REVISION OF THE TEXT

7 March 2018

# SUMMARY TABLE OF CHANGES

|  |  |
| --- | --- |
| **Date** | **Change** |
| 7 March 2018 | Data sheet reformatted  Section 4.7: Added statement on driving and using machinery.  Section 5.1: added Pharmacotherapeutic group and ATC code  Section 6.5 added container details  Section 8: Sponsor name and address changed to iNova Pharmaceuticals (New Zealand) Limited |