NEW ZEALAND DATA SHEET
PEVARYL 1% w/w Foaming Solution

1 PRODUCT NAME
PEVARYL 1% w/w foaming solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Econazole nitrate 1.0% w/w (as econazole base)

Excipients with known effect:

Benzyl alcohol

For a full list of excipients, see section6.1.

3 PHARMACEUTICAL FORM
Topical solution

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
PEVARYL Foaming Solution is indicated for the treatment of fungal skin infections and tinea.

4.2 Dose and method of administration
PEVARYL Foaming Solution should be applied to the wet body on three consecutive evenings. The foam should not be rinsed off but allowed to dry. The drug should develop its effect during the nights and may be removed the next morning by washing it off. Should fungal skin infection and tinea not be cured after a period of two weeks the treatment must be repeated. Repeat the course 1 month and 3 months after initial treatment to prevent relapse.

4.3 Contraindications
Although no specific contraindications are known, the product should not be used in patients known to be sensitive to any of the components.

4.4 Special warnings and precautions for use
Eyes

Avoid introduction of econazole foaming solution into the eyes.

Local irritation or hypersensitivity

Discontinue treatment if irritation or hypersensitivity occurs.

Lack of Response

If there is a lack of response to econazole, appropriate microbial studies should be carried out to confirm the diagnosis and rule out other pathogens. Intractable candidiasis may be the presenting symptom of unrecognised diabetes, thus appropriate urine/blood studies may be indicated in patients not responding to treatment.

Contraceptive diaphragms

Avoid contact with contraceptive diaphragms and this product since the rubber may be damaged by the preparation.

Prolonged use

Overgrowth of non-susceptible organisms may occur with prolonged use of any topical antimicrobial agent, including econazole.

4.5 Interaction with other medicines and other forms of interaction

Econazole is a known inhibitor of CYP3A4/2C9. However, due to the limited systemic availability after cutaneous application clinically relevant interactions are unlikely to occur, but have been reported for oral anticoagulants.

In patients taking oral anticoagulants, such as warfarin or acenocoumarol, caution should be exercised and the anticoagulant effect should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category A

Systemic absorption of econazole is low (< 10%) after topical application to the intact skin in humans. There are no adequate and well-controlled studies on adverse effects from the use of PEVARYL topical products in pregnant women, and no other relevant epidemiological data are available. No adverse effects of PEVARYL topical products on pregnancy or on the health of the foetus/newborn child have been identified from a limited number of post-marketing reports.

In animal studies, econazole nitrate has shown no teratogenic effects but was foetotoxic in rodents. The significance of this in humans is unknown.

Because there is systemic absorption, use of PEVARYL Topical Cream is not recommended during pregnancy.

Lactation

It is not known whether cutaneous administration of Pevaryl results in sufficient systemic absorption of econazole nitrate to produce detectable quantities in breast milk in humans.

A risk to the breast-fed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Pevaryl topical therapy taking into account the benefit of breast feeding for the child and benefit of therapy for the woman.

If Pevaryl is used while breast feeding, care should be taken to ensure the solution is not applied to the nipple or surrounding area.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

In a series of 948 patients, side effects, mainly burning sensation and pruritus were reported by 2.8%. Treatment was discontinued in 9 patients. Some local irritation may be encountered in eczematous areas.

There have been post-marketing reports of hypersensitivity, angioedema, rash, contact dermatitis, urticaria, blister and skin exfoliation.

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/

4.9 Overdose
No information is available concerning overdosage in humans as absorption and toxicity following topical application is low and no treatment should be necessary.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antifungals For Topical Use, Imidazole and triazole derivatives, econazole; ATC code: D01AC03.

In vitro activity:
Econazole nitrate has antifungal activity against a wide range of yeasts and fungi including *Candida albicans*. *C.guilliermondi*, *Torulopsis* spp. and the dermatophytes, *Trichophyton rubrum, T.mentagrophytes, Epidermophyton, Malassezia furfur*.

Mode of Action
PEVARYL appears to act by damaging the cell membrane and increasing its permeability. Synthesis of RNA is inhibited. Electron microscopy of *T. rubrum* shows changes in mitochondria (lysis of the cristae), degradation of the ribosomes and hypertrophy of the cytoplasmic membrane. In infections due to susceptible organisms cure rates of 80 to 90% were achieved. Average duration of treatment was 7 to 8 weeks although in some cases treatment had to be continued for longer periods.

5.2 Pharmacokinetic properties
Dermal absorption has been studied using titrated drug. Dermal application produces a high concentration of econazole in the horny layer, which exceeds the MIC for most fungal species. The necessary MIC is also reached in the upper layers of the epidermis (within 100 minutes of application). A small quantity is absorbed. There is some binding to human plasma proteins but no appreciable binding to erythrocytes. The main routes for elimination are via urine and faeces.

5.3 Preclinical safety data
In vitro studies have demonstrated that econazole is effective against Gram-positive bacteria and Trichomonas species.

Animal pharmacology
In rats and mice, oral econazole (40 mg/kg) has no parasympatholytic, parasympathomimetic, CNS stimulant; CNS depressant, analgesic, antiwrithing or toxic effects. In vitro, on isolated smooth muscle preparations and cardiac tissue, it is devoid of anticholinergic and antiserotonin activity, and alpha or beta adrenolytic effect. A non-specific, non-competitive antispasmogenic activity has been observed on guinea pig ileum. No inotropic effects were observed.

Acute toxicity
Oral LD50 in mice is 462 mg/kg, in rats 667 mg/kg and guinea pigs 272 mg/kg. LD50 in the dog is 217 mg/kg when administered i.p.

Chronic toxicity
Chronic (six month) toxicity has been studied in rats and dogs at doses up to 40 mg/kg (dog) and 60 mg/kg (rat). In rats slightly elevated creatinine values occurred in males dosed at 15 and 60 mg/kg. No signs of histological change were found in any group. In dogs autopsy findings revealed an increase in relative liver weight in the 40 mg/kg group. Histological changes in liver consisting of cloudy swelling, large vacuoles and hyaline deposits were seen at 10 and 40 mg/kg dose levels. Heart weights increased at 2.5 mg/kg dose levels.

Teratology
Econazole was administered to pregnant rats at doses of 40, 80, 160 mg/kg, & to pregnant rabbits at doses of 40 & 80 mg/kg. No teratogenic effects were produced in rat & rabbit foetuses. In various reproductive studies in female rats given oral doses of up to 40 mg/kg/day the following observations have been made at different dose levels: a decrease in pregnancy rate, an increase in the number of resorptions, an increase in the mean gestation time & reduced viability of the offspring at birth. With male rats an increase in the mating time necessary to achieve pregnancy was seen. In reproduction studies, rabbits given oral doses of up to 80 mg/kg/day, showed a dose related increase in resorption rate, & a decrease in average litter size was seen. However no effect on pregnancy rate was seen.

Tolerance
In the rabbit eye econazole provoked minor to moderate conjunctival responses which resolved within seven days. There is suggestive evidence from a study in 35 patients that econazole nitrate when applied to the skin is unlikely to cause reactions of a phototoxic or photosensitising nature.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzyl alcohol
Hydrochloric acid
Macrogol 6000 distearate
Miraspec TL/LDK
Polysorbate 20
Purified water
Sorbitan laurate

6.2 Incompatibilities
None stated

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at or below 25^0C.

6.5 Nature and contents of container
Sachet, 3 x 10 g

6.6 Special precautions for disposal

No special requirements

7 MEDICINE SCHEDULE

Pharmacy Only Medicine.

8 SPONSOR

iNova Pharmaceuticals (New Zealand) Limited
c/- Simpson Grierson
88 Shortland Street,
Auckland 1141

Toll-free number: 0508 375 394

9 DATE OF FIRST APPROVAL

28 May 1984

10 DATE OF REVISION OF THE TEXT

20 April 2018

SUMMARY TABLE OF CHANGES

Date	**Change**
20 April 2018	Data sheet reformat. Stand-alone data sheet created for Pevaryl Foaming Solution. Reference to other Pevaryl presentations removed. Change in sponsor name to: iNova Pharmaceuticals (New Zealand) Ltd Added pregnancy category A Added pharmacotherapeutic group and ATC code.