PRODUCT MONOGRAPH

TARO-MUPIROCIN

Mupirocin Ointment USP, 2%

Topical Antibiotic

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TARO-MUPIROCIN

Mupirocin Ointment USP 2%

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
topical	ointment 2% (20 mg/g)	polyethylene glycol 400 and polyethylene glycol 3350.

INDICATIONS AND CLINICAL USE

Taro-Mupirocin (mupirocin) is considered appropriate for the topical treatment of the following when caused by sensitive strains of staphylococcus and streptococcus species:

- impetigo
- superficially infected dermatoses
- lesions which are moist and weeping

For abrasions, minor cuts and wounds, the use of Taro-Mupirocin (mupirocin) may prevent the development of infections by sensitive Gram-positive organisms.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Taro-Mupirocin (mupirocin) and other antibacterial drugs, Taro-Mupirocin (mupirocin) should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Taro-Mupirocin (mupirocin) should not be given to patients with a history of hypersensitivity to mupirocin or any of the constituents of the preparation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

This mupirocin ointment formulation is not suitable for ophthalmic or intranasal use or use in conjunction with cannulae or at the site of venous cannulation.

General

When Taro-Mupirocin (mupirocin) is used on the face, care should be taken to avoid the eyes.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol based ointments, Taro-Mupirocin (mupirocin) should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

Prescribing Taro-Mupirocin (mupirocin) in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Ear/Nose/Throat

Taro-Mupirocin (mupirocin) is not suitable intranasal use.

Gastrointestinal

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhea during or after antibiotic use. Although this is less likely to occur with topically applied mupirocin, if prolonged or significant diarrhea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Ophthalmologic

Taro-Mupirocin (mupirocin) is not suitable for ophthalmic use. Avoid contact with the eyes. If contaminated, the eyes should be thoroughly irrigated with water until the ointment residue has been removed.

Renal

Moderate or severe renal impairment may occur upon absorption of large quantities of polyethylene glycol; please see General Information Section for further information.

Sensitivity/Resistance

Use of topical antibiotics occasionally allows overgrowth of non-susceptible organisms.
If this occurs, or irritation or sensitization develops, treatment should be discontinued and appropriate therapy instituted.

Sexual Function/Reproduction

There are no data on the effects of mupirocin on human fertility. Studies in rats showed no effects on fertility (see PART II Non-Clinical Information).

Skin
In the rare event of a possible sensitization reaction or severe local irritation occurring with the use of the product, treatment should be discontinued, the product should be wiped off and appropriate alternative therapy of the infection instituted.
As with other topical antibacterial products, prolonged use may result in overgrowth of non-susceptible organisms.

Special Populations

Pregnant Women: The safety of Taro-Mupirocin (mupirocin) in the treatment of infections during pregnancy has not been established. If administration to pregnant patients is considered necessary, its potential benefits should be weighed against the possible hazards to the fetus.

Studies in animals do not indicate reproductive toxicity (see PART II Non-Clinical Information).

Nursing Women: There is no information on the excretion of mupirocin in milk. Caution should be exercised when Taro-Mupirocin (mupirocin) is administered to nursing mothers. If a cracked nipple is to be treated, it should be thoroughly washed prior to breastfeeding or manual expression. If a treated cracked nipple is to be used for manual expression, milk from the affected breast should be discarded.

The safety and efficacy of Taro-Mupirocin (mupirocin) during lactation has not been demonstrated in animal or human models.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), including isolated reports.

Common and uncommon adverse reactions were determined from pooled safety data from a clinical trial population of 1573 treated patients encompassing 12 clinical studies. Very rare adverse reactions were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than true frequency.

Immune system disorders:

Very rare: Systemic allergic reactions including anaphylaxis, urticaria, angioedema, and generalized rash have been reported with Taro-Mupirocin (mupirocin) Ointment.

Skin and subcutaneous tissue disorders:

Common: Burning localized to the area of application.

Uncommon: Itching, erythema, stinging and dryness localized to the area of application.

Uncommon: Cutaneous sensitization reactions to mupirocin or the ointment base.

Post-Market Adverse Drug Reactions

Very Rare adverse events consist of systemic allergic reactions, including anaphylaxis, urticaria, angioedema, and generalized rash have been reported in patients treated with formulations of Taro-Mupirocin (mupirocin).

DRUG INTERACTION

Serious Drug Interactions

There are no known serious drug interactions noted for mupirocin.

Overview

There is no evidence of cross-resistance between mupirocin and other anti-microbial drugs.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

A small amount of Taro-Mupirocin (mupirocin) should be applied to cover the affected area 3 times daily for up to 10 days, depending on the response. The area treated may be covered with a gauze dressing if desired. Always wash your hands before and after applying.

Any product remaining at the end of treatment should be discarded.

Do not mix with other preparations as there is a risk of dilution, resulting in a reduction in the antibacterial activity and potential loss of stability of the mupirocin in the ointment.

Missed Dose

If an application of Taro-Mupirocin (mupirocin) is missed, apply as soon as you remember or when it is convenient, and then continue as before.

Administration

Populations

Renal impaired:
See WARNINGS AND PRECAUTIONS.

OVERDOSAGE

Overdosage has not been known to occur during topical therapy with mupirocin ointment.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mupirocin is a novel antibiotic produced through fermentation of *Pseudomonas fluorescens*. Mupirocin inhibits isoleucyl transfer-RNA synthetase, thereby arresting bacterial protein synthesis. Due to this particular mode of action, and its unique chemical structure, mupirocin does not show any cross- resistance with other clinically available antibiotics.

Mupirocin has bacteriostatic properties when applied locally at minimum inhibitory concentrations and bactericidal properties when applied at higher concentrations on the skin.

Pharmacodynamics

Mupirocin is a topical antibacterial agent showing *in vivo* activity against *Staphylococcus aureus* (including methicillin-resistant strains), *S. epidermidis* and beta-haemolytic *Streptococcus* species.

The *in vitro* spectrum of activity includes the following bacteria:

***Commonly* Susceptible *Species*:**

Staphylococcus aureus[1,2]
Staphylococcus epidermidis[1,2]
Coagulase-negative *staphylococci*[1,2]
Streptococcus species[1]
Haemophilus influenzae
Neisseria gonorrhoeae
Neisseria meningitidis
Moraxella catarrhalis
Pasteurella multocida.

[1]Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.
[2]Including beta-lactamase producing strains and methicillin-resistant strains

***Resistant Species*:**

Corynebacterium species
Enterobacteriaceae
Gram negative non-fermenting rods
Micrococcus species
Anaerobes

Mupirocin susceptibility (MIC) breakpoints for Staphylococcus spp.

Susceptible: Less than or equal to 1 microgram/ml

Intermediate: 2 to 256 micrograms/ml
Resistant: greater than 256 micrograms/ml

See PART II DETAILED PHARMOCOLOGY for further information.

Pharmacokinetics

Absorption:

Percutaneous Absorption

In man, a mean topical dose of 0.487 grams of radiolabelled mupirocin in the ointment base applied directly to the skin resulted in less than 0.24% systemic availability of the applied dose up to 120 hours after application. The amount of mupirocin-related material in blood and plasma were less than approximately 1.2 ng/mL. The penetration of mupirocin into the outer layers of skin was a mean of 2.71% of the applied dose 24 hours after application. Assessment of the persistence of mupirocin, as measured microbiologically, after four days of twice daily application, showed no evidence of persistence 48 hours after the last dose. It is concluded that mupirocin itself does not form a depot in the skin. However, it is evident that metabolites (primarily, biologically inactive monic acid) of mupirocin are present in the skin for up to 168 hours after application.

Mupirocin is poorly absorbed through intact human skin.

Effect of Occlusion

In an in vitro study using normal cadaver skin, application of mupirocin with occlusion brought about a five-fold greater penetration of mupirocin than without occlusion, although the amount of penetration was still very low (up to 0.33%).

Distribution:

Effect of Serum

Mupirocin was highly bound to serum protein (96.5% bound) and consequently, the activity of the compound was markedly reduced in the presence of human serum.

Metabolism:

Mupirocin is suitable only for topical application. Following i.v. or oral administration, or if mupirocin is absorbed (e.g. through broken/diseased skin) mupirocin is rapidly metabolized to inactive monic acid.

Excretion:

Mupirocin is rapidly eliminated from the body by metabolism to its inactive metabolite monic acid which is rapidly excreted by the kidney.

STORAGE AND STABILITY

Store at 15º – 25ºC.

SPECIAL HANDLING INSTRUCTIONS

Incompatibilities

None identified.

Use and Handling

Do not freeze.

Any product remaining at the end of treatment should be discarded.

Wash your hands after application.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each gram of Taro-Mupirocin (mupirocin) Ointment USP, 2%, contains 20 mg mupirocin in a bland water-soluble ointment base consisting of polyethylene glycol 400 and polyethylene glycol 3350.

Taro-Mupirocin (mupirocin) Ointment USP, 2%, is available in 15 gram and 30 gram tubes.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

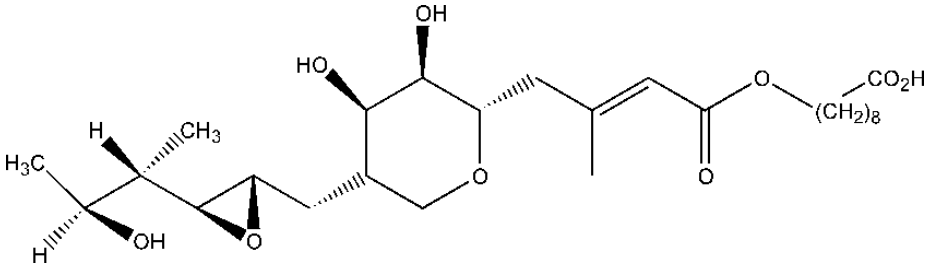
Drug Substance

Proper name: Mupirocin

Chemical name: (*E*)-(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid

Molecular formula and molecular mass: $C_{26}H_{44}O_9$ 500.62

Structural formula:



Physicochemical properties: A white to off-white crystalline solid. Freely soluble in acetone, chloroform, dehydrated alcohol and methanol; slightly soluble in ether and very slightly soluble in water. Melts between 70º and 76.5ºC.

CLINICAL TRIALS

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study compared the safety and efficacy of Taro-Mupirocin Ointment with that of Bactroban® Ointment 2% (GlaxoSmithKline Inc., U.S.A.), in patients who had a clinical diagnosis of impetigo contagiosa or uncomplicated blistering impetigo and who were 18 months of age or older. A thin layer of ointment was applied to the affected areas 3 times daily for 7 days (21 applications). The primary efficacy endpoint was the clinical response 7 days post-treatment or at early termination. Clinical success was defined as sufficient resolution of signs and symptoms of infection such that no additional antibiotic therapy was required to treat impetigo, and a SIRS (Skin Infection Rating Scale) score of <2 for each of erythema/inflammation and itching/pain. Safety was assessed by adverse events, early terminations, extent of exposure and concomitant medications.

Five hundred and sixty-five (565) patients were randomized, 222 to Taro-Mupirocin Ointment 2%, 224 to Bactorban® Ointment 2% and 119 to the Placebo group. The mean age was 11.9 years (range 1 – 62 years). The primary efficacy analysis, clinical response 7 days post-treatment in the per-protocol analysis set, demonstrated noninferiority of Taro-Mupirocin Ointment 2% versus Bactroban® Ointment 2% (see Table 1). Results for the intent-to-treat analysis set 7 days post-treatment were similar.

Table 1 Comparison of Clinical Response and Assessment of Noninferiority 7 days post-treatment for the per-protocol Analysis Data Set for Taro's Vehicle, Taro-Mupirocin Ointment and Bactroban® Ointment 2% (U.S.) Reference Product

Product	Clinical Success %	N	95% CI Taro vs. Bactroban®	p Value Active vs. Vehicle
Taro	96.9	191	-1.2-8.5*	p<0.0001
Bactroban®	93.2	191		p<0.0001
Vehicle	64.0	89		
		471		

*Since the 95% CI lay entirely above -13%, Taro-Mupirocin was declared noninferior to Bactroban® (U.S.) in the treatment of impetigo.

One hundred and twenty-three (21.8%) patients reported 163 adverse events over the duration of the study: 15.8% of patients with Taro-Mupirocin, 19.6% of patients with Bactroban®, and 37.0% of patients with Placebo. The most commonly reported adverse events were viral infection, furuncle, upper respiratory tract infection and laceration. A small number of patients experienced application site burning, bleeding or pain; these adverse events were reported in all treatment groups.

Bridging Study

A bridging study compared the antimicrobial activity of Taro-Mupirocin Ointment 2% with that of Bactroban® Ointment 2% marketed in Canada, the U.K. and the U.S. in reducing the viability of *Staphylococcus aureus* on experimentally-contaminated skin of the forearms of healthy adult subjects. *Staphylococcus aureus* was chosen for this assay because of its clinical relevance and because it generally requires as high or higher a MIC for efficacy as does mupirocin sensitive *Streptococcus*. Mean kill rates for Taro-Mupirocin 2% and Canadian Bactroban® Ointment are detailed in Table 2. This study demonstrated that Mupirocin Ointment 2% manufactured by Taro Pharmaceuticals Inc. (Canada) is therapeutically equivalent to Mupirocin Ointment 2% (Bactroban®) marketed by GlaxoSmithKline Inc. (Canada).

Table 2 Comparison of Mean Kill Rates Normalized to Control for Taro-Mupirocin Ointment 2%, and Canadian, U.S. and U.K. Bactroban® Ointment 2% Reference Products

Kill Rates ± S.D. (%)		N	Ratio (%)	90% CI
Taro	**Canada**		**Taro/Canada**	**Taro/Canada**
94.5 ± 12.0	**97.7 ± 5.7**	**71**	**96.7**	**94.6 – 98.9**

Taro 94.5 ± 12.0	U.S. 98.4 ± 3.0	71	Taro/U.S. 96.0	Taro/U.S. 93.8 – 98.3
Taro 94.5 ± 12.0	U.K. 97.5 ± 7.5	71	Taro/U.K. 96.9	Taro/U.K. 94.7 – 99.1

Study Design and demographics

Table 3 provides the study design and demographics for 4 clinical studies. .

Study 2095-01X was a double-blinded, vehicle controlled, parallel-group Phase III studies that evaluated the efficacy and safety of Mupirocin ointment 2% for the treatment of secondary infections of the skin in adult subjects.

Study 20925-02X was a double-blinded, vehicle controlled, parallel-group Phase III studies that evaluated the efficacy and safety of Mupirocin ointment 2% for the treatment of secondary infections of the skin in pediatric subjects.

Study 20925-03X/A was a double-blinded, vehicle controlled, parallel-group Phase III study that evaluated the efficacy and safety of Mupirocin ointment 2% for the treatment of primary infections of the skin in adult and pediatric subjects.

Study 20925-04X assessed the efficacy and safety of Mupirocin ointment 2% in an open label (no vehicle control) study for the treatment of primary and secondary infections of the skin in children.

All protocols required patients to be treated with Mupirocin ointment 2% 3 times a day for 3-9 days (up to 12 days was permitted if scheduling did not permit subject return at scheduled ($\pm$1) day 8 evaluation). Bacteriological and clinical evaluations were recorded before and after therapy. Subjects returned mid-treatment (day 4 $\pm$1) for clinical assessment, at which time the therapy could be halted if the infection had healed or worsened. Patients were allowed no less than 3 days or more than 12 days of therapy to be evaluable for efficacy.

Table 3- Summary of clinical study design and patient demographics

Study #	Trial design	Infection	Duration	Age Range	Subjects (n)	Gender M/F	Outcomes measured
20925-01x	Double-blind vehicle controlled	Secondary infections of the skin	3 times daily for 3-9 days	$\geq$ 12 years	979	512/467	Clinical efficacy rates: cured/improved/failed Pathogen eradication: failure/success
20925-02X	Double-blind vehicle controlled	Secondary infections of the skin	3 times daily for 3-9 days	$\leq$ 12 years	51	25/26	Clinical efficacy rates: cured/improved/failed Pathogen eradication: failure/success

20925-03X/A	Double-blind vehicle controlled	Primary infections of the skin	3 times daily for 3-9 days	No age restrictions	163	82/81	Clinical efficacy rates: cured/improved/failed Pathogen eradication: failure/success
20925-04X	Open label, no vehicle control	Primary and secondary infections of the skin	3 times daily for 3-9 days	0.1 to ≤ 13 years	139	63/76	Efficacy and safety

Study Results

Table 4 provides a summary of the clinical study results

Table 4 – Summary of clinical study results

Study #	Primary Endpoints	Associated value and statistical significance for Drug (mupirocin 2% w/w)	Associated value and statistical significance for Placebo or active control	Statistical Analysis
20925-01x	Clinically beneficial response (cure, improvement)	91% (p<0.001)	78% (p<0.001)	Chi-square test
	Bacteriologically beneficial response	86% (p<0.001)	53% (P<0.001)	Chi-square test
20925-02X	Clinically beneficial response (cure, improvement)	95% (p<0.05)	71% (p<0.05)	Chi-square test
	Bacteriologically beneficial response	97% (p<0.001)	46% (p<0.001)	Chi-square test
20925-03X/A	Clinically beneficial response (cure, improvement)	95% (p<0.01)	78 % (p<0.01)	Chi-square test
	Bacteriologically beneficial response	94% (p<0.001)	62% (p<0.001)	Chi-square test

20925-04X	Clinically beneficial response (cure, improvement) Bacteriologically beneficial response	99% 99%	N/A	N/A

Study 20925-01X: adult patients

A clinically beneficial response (cure, improvement) was seen in 91% of patients (n=422) receiving Mupirocin ointment 2% and in 78% of patients receiving vehicle (n=392)($p<0.001$). A bacteriologically beneficial response was achieved in 86% pathogens from patients in the Mupirocin ointment 2% group (n=553) and in 53% pathogens from the vehicle group (n=524)($p<0.001$).

Study 20925-02X: paediatric patients

A clinically beneficial response (cure, improvement) was seen in 95% of patients (n=20) receiving Mupirocin ointment 2% and in 71% of patients receiving vehicle (n=17)($p<0.05$). A bacteriologically beneficial response was achieved in 97% of pathogens from patients in the Mupirocin ointment 2% group (n=30) and in 46% pathogens from the vehicle group (n=24)($p<0.001$).

Study 20925-03X/A: no age restrictions
A clinically beneficial response (cure, improvement) was seen in 95% of patients (n=61) receiving Mupirocin ointment 2% and in 78% of patients receiving vehicle (n=63)($p<0.01$). A bacteriologically beneficial response was achieved in 94% of pathogens from patients in the Mupirocin ointment 2% group (n=79) and 62% of pathogens from the vehicle group (n=82)($p<0.001$).

Study 20925-04X: paediatric patients

A clinically beneficial response (cure, improvement) was seen in 99% of patients receiving Mupirocin ointment 2% (n=127). A bacteriologically beneficial response was achieved in 99% pathogens from patients receiving Mupirocin ointment 2% (n=138).

DETAILED PHARMACOLOGY

MICROBIOLOGY

Mupirocin is active against those micro-organisms responsible for the majority of skin infections. It is particularly active against staphylococci, including methicillin-resistant strains. It is also active against many Gram-negative bacteria as a result of the high concentrations achieved after topical administration. Most strains of *Morganella morganii*, *Serratia marcescens* and *Pseudomonas aeruginosa* are resistant. It is not active against most anaerobic bacteria, mycobacteria, mycoplasma, chlamydia, yeast, and fungi. The *in vitro* activity of mupirocin against strains of various organisms is presented in Table 5.

TABLE 5: ***In vitro activity of mupirocin***

LABORATORY SPECIES	***MIC (∝g/mL)***
Aerobic Gram-Positive	
Staphylococcus	
S. epidermidis	*.0.25*
S. haemolyticus	*0.5*
S. hominis	*0.5*
S. saprophyticus	*.0.25*
S. aureus ATCC 25923	*0.5*
S. aureus NCTC 6571	*.0.25*
S. capitis	*.0.06*
S. cohnii	*.0.12*
Streptococcus	
S. pyogenes	*.0.12*
Streptococcus species Group C	*0.25*
Streptococcus species Group G	*0.25*
S. agalactiae	*.0.12*
S. pneumoniae	*0.5*
S. durans	*32*
S. bovis	*128*
S. mitis	*.0.25*
Enterococcus	
E. faecium	*32*
E. faecalis	*64*
Corynebacterium	
C. xerosis	*>128*
C. minutissimum	*>128*
Corynebacterium species Group JK	*>128*
Bacillus subtilis	*.0.25*
Micrococcus	
M. luteus	*>1024*
M. varians	*>1024*
M. nishinomiyaenosis	*>1024*
Erysipelothrix rhusiopathiae	*.16*
Listeria monocytogenes	*16*
Anaerobic Bacteria	
Peptostreptococcus anaerobius	*>128*
Peptostreptococcus asaccharolyticus	*>128*
Clostridium	
C. difficile	*>1024*
C. sporogenes	*>1024*
C. tertium	*>1024*
Propionibacterium	
P. acnes	>1024
P. granulosum	>1024
P. avidum	>1024
Aerobic Gram-Negative	
Neisseria gonorrhoeae	0.06

Haemophilus influenzae	0.06
Pasteurella multocida	0.12
Aerobic Gram-Negative	
Escherichia coli	128
Klebsiella	
K. pneumoniae	128
K. oxytoca	256
Providencia	
P. rettegeri	>1024
P. stuartii Harding	32
Acinetobacter anitratus	>1024
Pseudomonas aeruginosa	>1024
Morganella morganii	>1024
Serratia marcescens	>1024
Anaerobic Bacteria	
Bacteroides fragilis	>1024

Effect of Inoculum Size

There is only a slight effect of inoculum size on mupirocin's minimum inhibitory concentrations (MIC's). For *Staphylococcus aureus*, inocula ranging from 10^6 cells/mL (undiluted) to 10 cells/mL (10^5 dilution) resulted in a two- to four-fold variation in the MIC values.

Effect of Composition and pH of Medium

The antibacterial activity of mupirocin was not influenced by the composition of the medium. The MIC values of mupirocin were generally two- to four-fold lower at acid pH (6.0) and two- to four-fold higher at alkaline pH (8.0) than those observed in the medium of normal pH (7.4).

Minimum Bactericidal Concentrations

The MIC values of mupirocin against strains of *Staphylococcus aureus* ranged from 0.12 mcg/mL to 2.0 mcg/mL and the MBC values from 0.5- >128 mcg/mL. In most cases, the MBC values were from eight- to thirty-two-fold higher than the corresponding MIC values.

Development of Resistance

The selection of mupirocin-resistant variants of *Staphylococcus aureus* after repeated exposure to increasing concentrations of the compound, occurred in a slow and stepwise fashion.

TOXICOLOGY

Acute Toxicology

The acute toxicity of mupirocin* was determined in mice and rats dosed orally, subcutaneously and intravenously.

*The dose level was in terms of pure sodium salt.

Acute Toxicity

Species	Route	Sex	LD_{50} (mg/kg)
Mice	Oral	M	>5000
		F	>5000
Rats	Oral	M	>5000
		F	>5000
Mice	s.c.	M	4000 - 5000
		F	4000 - 5000
Rats	s.c.	M	>5000
		F	>5000
Mice	i.v.	M	1638 - 2048
		F	1638 - 2048
Rats	i.v.	M	1310 - 2560
		F	1310 - 2560

All animals were observed for 14 days. Animals dosed orally remained in healthy condition throughout the study and there were no abnormal findings at post-mortem. Subcutaneously dosed animals showed injection site irritancy with scab formation. Mottled kidneys were found in all surviving mice and in half of those which did not survive. Animals dosed intravenously were observed to convulse immediately after dosing and sedation was evident in most animals. Mottled or pale kidneys were found in many of those surviving.

Subacute Toxicity:

Rats:

Mupirocin was administered for 14 days to 3 groups of rats each comprising 10 males and 10 females. Two groups were subcutaneously (s.c.) dosed at 100 or 500 mg/kg/day and the third group was orally (p.o.) dosed at 100 mg/kg/day. A fourth and fifth group served as controls and the sixth group of 5 males and 5 females was the health screen. Clinical conditions and laboratory determinations were carried out. There were no treatment related deaths during the study. Injection site damage and alopecia was seen in all animals in the high subcutaneous dose group. Body weight gain, food consumption and water intake were unaffected by treatment. High s.c. dosed animals had slight decreases in haemoglobin, PCV (packed cell volume) and red cell count together with an increase in total leucocyte count and absolute neutrophil count. Orally dosed females had slightly increased haemoglobin and red cell counts and decreased MCV (mean corpuscular volume). Subcutaneously high dosed animals had reductions in SAP (serum alkaline phosphatase) activity, total protein, albumin A/G ratio together with increases in SGPT activity. The males also exhibited increased glucose and decreased potassium. Females receiving 500 mg/kg s.c. exhibited increased urine osmolality on day 13. Macroscopic examination revealed that there was a dose related increase in severity and extent of injection site irritancy. Increases in adrenal weights were noted in males from the high dose s.c. and orally dosed groups. The relative thymic weight in high dose s.c. males was reduced by 13% compared to controls. Significant increases of 31% and 20% were seen in the relative splenic weights of the male and female 500

mg/kg (s.c.) groups respectively and of 13% in the female oral dose group. Histological examination of the kidneys revealed minimal chronic inflammatory cell infiltration and was associated with occasional distended tubules and tubules characterized by the basophilic staining of the cells of the epithelium in the high dose s.c. and oral dose groups.

Squirrel Monkeys:

Mupirocin was administered to four groups of squirrel monkeys each comprising of 2 males and 2 females. Two groups were dosed orally at 50 or 150 mg/kg/day for 14 days and two groups were dosed intramuscularly at 50 or 150 mg/kg/day for 14 days. A fifth group served as control.
Clinical conditions and laboratory determinations were monitored and post-mortem and histopathologic determinations were carried out. There were no deaths during the study and no clinical adverse signs. Body weights and food intake were unaffected by treatment. Haematology, urinalysis and blood chemistry revealed no treatment-related effects. At post-mortem examinations, no effects of the drug on organ weights was noted. Histopathological studies showed mild involution of the thymus in some treated animals. Examination of the injection site soft tissues of the i.m. dosed groups revealed mild to moderate irritation reactions.

Chronic Toxicity:

Rats:

Mupirocin in a polyethylene glycol vehicle was applied topically to a shaved unabraded area on the dorsum of 3 groups of rats. Each group was comprised of 10 males and 10 females dosed at 10, 20 or 40 mg [1]pfa/kg/day in dose volumes of 0.5 mL/kg, 1 mL/kg and 2 mL/kg respectively. Dosing was conducted daily for 28 days. A fourth and fifth group served as control and vehicle control. Five male and five female rats were added to each of the control groups and the high dose groups to determine effect of drug withdrawal. At the end of the treatment period these three groups were left undosed for a period of two weeks before sacrificing. Clinical condition and laboratory determinations were monitored and post-mortem and histopathological determinations were carried out. In the final 4 days off-dose the high dose treated females gained less weight than those undosed controls (33%) and vehicle controls (20%). This was of uncertain significance. Blood chemistry showed slight decrease in glucose in the male intermediate dose group at day +29. Increases in glucose were noted in intermediate and high dose male groups and an increase in urine volume with decreased osmolality in the intermediate dose female group. Histological examination revealed vacuolation of parietal cells in females in all dose groups. This change was not observed in the high dose group after the off-dose period.

[1] pfa – pure free acid

Rabbits:

Mupirocin in a cream base was applied topically to a shaved abraded area on the back of 3 groups of rabbits. Each group was comprised of 5 male and 5 female animals dosed at 10, 20 or 40 mg pfa/kg/day in dose volume of 0.5 mL/kg, 1 mL/kg and 2 mL/kg respectively. Treatment was conducted daily for 30 days (6 hr/day under an occlusive dressing). A fourth and fifth group served as control and vehicle control. Two male and two female animals were added to each of the control groups and the high dose group to determine the effect of drug withdrawal. At the end of the treatment period these three groups were left undosed for a period of two weeks before sacrificing. Clinical conditions and laboratory determinations were monitored and post-mortem and histopathologic determinations were carried out. One male from the intermediate dose group died. Necropsy revealed a large abscess on the serosal surface of the colon. Similar body weight gains were recorded for all groups throughout the study, however, marked increases in body weight gains were noted in all animals during off-dose period. Slight skin irritation (erythema, oedema and atonia) was noted in all treatment groups including vehicle control animals. Macroscopic pathology revealed minimal acanthosis of the epidermis and/or leucocyte accumulation in the statum corneum.

Rats:

Mupirocin was administered daily by the subcutaneous route to 3 groups of rats each comprising 15 males and 15 females at doses of 10, 40 or 100 mg/kg/day for 3 months. A fourth group (control) received sterile saline. Five male and 5 female rats were added to each of the high dose and control groups to determine the effect of drug withdrawal. At the end of the treatment period, these two groups were left undosed for 28 days. Clinical conditions and laboratory determinations were monitored and post-mortem and histopathological determinations were carried out. One female was killed in extremis on day 3 and replaced. Autopsy revealed no treatment related causes. One low dose female and one intermediate dose male died under anaesthetic and a further female was killed in extremis following accidental injury. Alopecia and scab formation wereseen at the injection sites of high dose males from day 7 onward. Mild signs of sialodacryoadenitis were noted in all groups from day 42. Weight gain in high dose females was reduced after 6 weeks of dosing but was comparable to control by the end of dosing period. In intermediate dose males, weight gain was 14% overall greater than controls. Low dose females gained 63% more than controls in the final 5 weeks of dosing. Food intake was greater in intermediate dose males. Water intake of males increased during week four.

Female rats had decreased water consumption in week 4 but low dose females had significant increase in week 12. During “off-dose”, females in the high dose group had slightly less water consumption than controls. There were no significant haematologic changes except for a slight reduction in red cell parameters in treated females at the interim examination. Increases in ALT (alanine amino-transferase) were noted intermediate and high dose males. Decreased total protein and albumin in high dose males and increased A/G ratio in low dose males was also noted. Increases in urine volume occurred in high dose males and females. Macroscopic examinations revealed a treatment related incidence of injection site irritation. After treatment period, there was an increase in spleen weight in the high dose females. A significant increase in liver weights of high dose level females at this time showed reversal upon drug withdrawal.

Dogs:

A similar study was carried out in beagle dogs. Mupirocin was administered daily by the route to 3 groups of dogs each comprising 4 males and 4 females at doses of 5, 10 and 20 mg/kg/day. (These doses were reduced from 10, 40 and 80 mg/kg respectively on day 4.) A fourth group (control) received sterile saline. Two males and two females were added to each of the high dose and control groups to determine the effect of drug

withdrawal. At the end of the treatment period, these two groups were left undosed for a period of 28 days. Immediate reaction to treatment in the form of muscular weakness and convulsions was evident in several dogs at levels of 40 and 80 mg/kg. On lowering of these dose levels, reactions continued until day 6 until a reduced injection rate was introduced. There were no mortalities. A decrease in total leucocyte count was seen in most intermediate and high dose males and most females in all dose groups. Blood chemistry revealed increases in A/G ratios in 4 high dose males at terminal examination. Analysis of ECG's from dogs showing adverse reactions at onset of dosing showed pronounced bradycardia, sometimes with tachycardia with onset, during or immediately after dosing and recovery within 2 minutes. Macroscopic, pathologic and histopathologic examinations revealed no changes considered to be related to treatment.

Carcinogenesis/Mutagenesis:

Carcinogenesis:

Carcinogenicity studies with mupirocin have not been conducted.

Genotoxicity:
In non-mammalian cell *in vitro* assays, mupirocin produced weak positive results in *Escherichia coli* repairable genetic damage tests and in *Salmonella typhimurium* TA98 in reverse mutation assays, both in the absence of metabolic activation. Other non-mammalian cell assays including an Ames assay with *Salmonella. typhimurium*, a gene conversion test with *Saccharomyces cerevisiae*, and a forward mutation test with *E. coli* were negative.

In an in vitro mammalian gene mutation assay (MLA), no increase in mutation frequency was observed in the absence of metabolic activation. In the presence of metabolic activation, small increases in mutation frequency were observed at highly cytotoxic concentrations.

However, no treatment-related effects were observed in, yeast cell assays for gene conversion/mutation, an in vitro human lymphocyte assay or in an in vitro unscheduled DNA synthesis (UDS) assay.

Furthermore, an in vivo mouse micronucleus assay (chromosome damage) and a rat Comet assay (DNA strand breakage) were negative, indicating the small increases observed at highly cytotoxic concentrations in vitro do not translate to the in vivo situation.

Reproductive Toxicology:

Fertility and General Reproductive Performance:

Mupirocin was administered subcutaneously to 3 groups of rats, each comprising 28 males and 28 females, at doses of 10, 40 and 100 mg/kg/day. A fourth group (control) received the vehicle (sterile saline). Male rats were dosed daily from 10 weeks prior to mating until successful littering by F_0 females. Female rats were treated daily from day 15 prior to mating until day 24 post-partum or until selected for caesarean section on gestation day 21. On gestation day 21, 14 females/group were sacrificed and a caesarean section carried out and the remaining 14/group were allowed to litter normally. From these litters a total of 28 males and 28 females were selected to form the F_1 generation. They were mated at 11 weeks of age and the procedures followed were comparable to the F_0 generation. One female animal in the high dose group was killed, not due to a direct effect of treatment. Alopecia and scabbing at injection sites was seen in the female intermediate dose group and in all animals at the high dose level. Top dose females had a reduction in body

weight gains during the latter part of gestation. Fertility and general reproductive performance were not affected by treatment.

In the litters of females sacrificed for caesarean section there were treatment related trends in reduction in general cranial ossification. Pups from females allowed to litter were unaffected by parental treatment. The F_1 generation showed no signs of physical condition ascribable to treatment of the F_0 generation. One female in the low dose group was killed following total litter loss on day 2 post-partum. Before pairing females derived from treated parents showed significant increases in body weight gains compared to animals from control parents. The rate was similar in all groups during gestation but significantly reduced in the intermediate and high dose group animals during lactation. Males derived from high dose F_0 generation had slightly poorer recall ability. In the F_1 animals allowed to litter the only effect recorded in the pups was a significant reduction in the percentage of females in the top dose group to have developed the static righting reflex.

Teratology:

Three groups of 15 female rabbits were mated and mupirocin was then subcutaneously administered from day 6 to day 18 of gestation at doses of 10, 40 and 160 mg/kg/day. A fourth group (control) was dosed with physiological saline (vehicle). On day 29 of gestation, the animals were sacrificed and caesarean section carried out. Orange colouration of the urine was seen in the majority of high dose animals and in some intermediate dose animals. Four high dose animals showed palpable thickening and tightening of the skin and associated abnormal gait. Three of these affected animals aborted and were killed before day 29. One other animal in the high dose group and one in the control group also aborted but survived until termination of study. Higher incidence of anorexia and reduced fecal output during dosing or post-dosing periods was noticed in the intermediate and high dose groups. Maternal weight gain was impaired in the high dose group. A slightly lower mean number of corpora lutea was recorded in all test groups and pre-implantation loss was higher in low and intermediate dose groups resulting in lower number of implantations but these were not statistically significant. Autopsy of high dose animals revealed dose-related injection site reactions with subcutaneous haemorrhage, dermal thickening and subcutaneous white discolouration in the dorsal area. There were no significant changes in litter parameters and incidences of major malformations, minor anomalies and skeletal variants were unaffected by treatment.

In a preliminary developmental study in rats, there was no evidence of embroyotoxicity, embryolethality or teratogenicity at subcutaneous doses up to 375 mg/kg/day.

Perinatal and Postnatal Studies:

Mupirocin was administered subcutaneously to 3 groups, each comprising 22 pre-mated rats, at doses of 11.1, 44.2 or 106.7 mg/kg/day from day 15 of gestation to day 25 post-partum. A fourth group (control) was dosed with sterile saline. One parent animal in the low dose group was killed following extreme dystocia. Local irritation in the form of swelling and/or scabbing at the injection site was seen in all dose levels. Pregnancy rate and implantation index and length of gestation was comparable for all groups. Autopsy of parent animals revealed an increased number of injection site reactions in the form of subdermal haemorrhaging, scabbing and alopecia in the high dose group. These incidences were less severe in the low and intermediate dose groups. There was no evidence of treatment related effect on the general condition of the offspring. Group mean litter size was slightly lower than control in the intermediate dose group and markedly lower in the higher dose group. There was a slight reduction in the viability index (at day 4) of the high dose animals with more minimal effects seen in the remaining treated and control groups. The F_1 generation parameters revealed no other meaningful differences or dose related trends in litter observations, behavioural and developmental indices.

Irritation and Sensitization Studies:

Animal

Rabbits:

The area on the back of six female rabbits was clipped free from hair. The left side was left intact, the right side was abraded, penetrating the stratum corneum but not damaging the underlying dermis. Mupirocin in an ointment base was then applied to both sides at a dose of 0.5 mL and covered with gauze for a period of 24 hours. Dressings were then removed and skin wiped free of ointment. Observations made at 24 hours and 72 hours after treatment revealed no adverse skin reactions.

Guinea Pigs:

An area on either side of the trunk of 50 male guinea pigs was clipped free of hair and groups were dosed as follows:

Group 1, comprised of 20 animals was dosed with 0.5 mL mupirocin in a polyethylene glycol base.

Group2, control was comprised of 20 animals and dosed with 0.5 mL base formulation.

Group 3, positive control was comprised of 10 animals and dosed with 0.5 mL DNCB (0.1% w/v 1-chloro-2,4-dinitrobenzene).

Each group was dosed a total of 10 times, each 3 days apart at a different skin site. Fourteen days after the last dose, each group received a challenge application. Skin reactions were assessed 24 hours and 48 hours after each induction and challenge application. One animal in group 1 was killed on day 6 following a prolapse and another animal died on day 18. No abnormalities were noted at necropsy. One control animal died on day 24. No abnormalities were noted at necropsy. No adverse skin reactions were noted in any of the control groups during the induction period. Twenty-four hours following the challenge application, five animals in group 1 showed very slight erythema. This had disappeared in all but 1 of the animals at the 48 hour observation. Following the challenge application in group 3, all animals produced skin responses in the form of slight to well-defined erythema and slight oedema. These responses were increased slightly at the 48 hour observation.

Human:

Mupirocin in a polyethylene glycol base was applied to the arms of 80 volunteers 2 or 3 times daily for 21 or 28 days at doses of approximately 1 mL per application on a site 5 cm x 5 cm. A further 19 subjects applied the base only in the same manner. After 7 or 14 days without treatment, a rechallenge was made with another similar application. Haematology, clinical chemistry, urinalysis and any reactions to the applications were monitored throughout the study. One subject receiving active drug demonstrated slight redness at the application site on day 2. Another subject developed a rash over the dosing site 18 days after the rechallenge. This was not considered an allergic response to the application. There were no drug related changes in clinical chemistry, haematology or urinalysis.

Mupirocin in a polyethylene glycol base was applied to the arms of 107 volunteers twice daily for 28 days at doses of 0.1 mL/application to a site 5 cm x 5 cm. The site was then covered with an occlusive dressing. The application sites were exposed to air up to 1 hour/day. A further 16 subjects received the base only in a

similar manner. Seven to 14 days after dosing, a patch sensitization test was carried out, leaving the patch in place for 48 hours. Haematology, clinical chemistry, urinalysis and any reactions to dosing were regularly monitored for the duration of the study. One subject receiving active material withdrew from the study because of pruritis under the occlusive dressing. A number of subjects experienced itching related to the occlusive dressing. Eight subjects receiving active material developed transient rashes at the application sites, however, 5/8 had not removed the occlusion daily. Five subjects experienced burning, itching or aching pains in association with the application but without cutaneous rashes. The patch sensitization test did not result in a reaction to the application. There were no drug related changes in haematology, clinical chemistry or urinalysis parameters.

Seventy-eight subjects who had received mupirocin in the previous 1 ½ - 35 months participated in a rechallenge test. Each subject had 0.1 mL of 2% mupirocin ointment applied to an "A1-test" disc, placed on the arm and occluded for 48 hours. None of these subjects showed evidence of sensitization.

Twenty-five volunteers had 2% mupirocin ointment applied to sites on their forearms, which had been previously treated with 1.0% sodium lauryl sulphate. Each subject was treated with 0.3 grams for five 48 hour periods. Ten days later a challenge application was applied to a different site which had been pre-treated with 10.0% aqueous solution of sodium lauryl sulphate. There were no instances of irritation or contact sensitization during the application period or after challenge with either material.

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PART III: CONSUMER INFORMATION

Taro-Mupirocin
Mupirocin Ointment USP, 2%)

This leaflet is part III of a three-part "Product Monograph" published for Taro-Mupirocin approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Taro-Mupirocin. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Taro-Mupirocin (mupirocin) is used for:
- The treatment of impetigo.
- The treatment of minor bacterial skin infections.
- The prevention of infection in minor cuts and wounds

What it does:
Taro-Mupirocin is an antibiotic. It helps heal minor cuts and wounds in the skin and helps prevent or control minor skin infections by killing or controlling the growth of the bacteria.

When it should not be used:

Taro-Mupirocin should not be used:
- Do not use Taro-Mupirocin to treat infections in or near the eyes, nostrils or mouth.
- If you have a tube that is inserted surgically into the body that allows fluid to enter or escape, do not use Taro-Mupirocin around it.
- If you are allergic to mupirocin or any of the other ingredients in Taro-Mupirocin (see "What the important non-medicinal ingredients are" section). Signs of an allergic reaction may include local irritation, an itchy skin rash, shortness of breath and swelling of the face or tongue.
- Avoid applying to large areas of broken or damaged skin especially if you have problems with your kidneys.

What the medicinal ingredient is:
Mupirocin contains mupirocin 2% (w/w).

What the important nonmedicinal ingredients are:
polyethylene glycol 400 and polyethylene glycol 3350.

What dosage forms it comes in:
Ointment: mupirocin 2% (w/w)
Taro-Mupirocin is available in 15 g and 30 g tubes. The cap comes with the piercing tip.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Taro-Mupirocin is not suitable for eyes or into nose use or use in conjunction with tube insertion into the body or body cavity or at the site of intravenous injection.

Your doctor will have asked you many questions about your health, lifestyle and medications before recommending Taro-Mupirocin. That is why it is very important you tell your doctor all such information. If you have forgotten to tell your doctor about any of the following, call your doctor or pharmacist before using this medication (or any medicine):

- You are allergic to mupirocin or polyethylene glycol.
- You have problems with your kidneys or have any renal problem.
- You are pregnant or plan to become pregnant.
- You are breastfeeding your baby. If you are applying Taro-Mupirocin to the nipple area, wash thoroughly before breastfeeding or manual expression of milk.
- You're taking any other medicine, if you've taken any recently, or if you start taking new ones. This includes medicine you bought without a prescription and natural health products.
- You are a child (younger than 12 years) or older than 65 years of age.

This medicine is for external use only.
Discontinue use and consult with your doctor if condition worsens or if irritation occurs or infection has not cleared after 10 days.

Antibacterial drugs like Taro-Mupirocin treat **only** bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, Taro-Mupirocin should be used exactly as directed. Misuse or overuse of Taro-Mupirocin could lead to the growth of bacteria that will not be killed by Taro-Mupirocin (resistance). This means that Taro-Mupirocin may not work for you in the future. Do not share your medicine.

Long term use may result in development of antibiotic resistance.

If this medicine does get into your eyes, wash them out immediately, with large amounts of cool tap water.

INTERACTIONS WITH THIS MEDICATION

There are no known drug interactions noted for Taro-Mupirocin

PROPER USE OF THIS MEDICATION

Usual dose:
Follow your doctor's instructions about how and when to use Taro-Mupirocin. Wash your hands before and after applying Taro-Mupirocin.

Squeeze a small amount onto your finger-tip and apply to the affected area 3 times each day for up to 10 days. Your doctor may tell you to cover the area with a dressing after you have applied Taro-Mupirocin.

Do not mix Taro-Mupirocin with other lotions, creams, or ointments. This may dilute Taro-Mupirocin, which may affect your treatment.

It is important that you take the full course of Taro-Mupirocin until the infection has fully cleared up or for up to 10 days. Don't stop early as your symptoms may disappear before the infection is fully cleared.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If an application of Taro-Mupirocin is missed, apply as soon as you remember or when it is convenient, then continue as before.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side-effects with Taro-Mupirocin are generally mild. A few people may experience some unwanted effects. These may include stinging or tingling (which occurs on the area of the skin where Taro-Mupirocin has been applied). Allergic responses (such as rash, local pain or swelling) have been reported rarely.

If any of these side-effects are troublesome or you are concerned about any other problems while you are using Taro-Mupirocin, tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Burning**	√		
Uncommon	**Itching**	√		
	Skin Dryness	√		
	Skin Redness	√		
	Skin Inflammation and itchiness (Cutaneous Sensitization)		√	√
Very Rare	**Allergic Reaction** symptoms: Hives; itchy rash, swelling of the face, lips mouth, tongue or throat which may cause difficulty in swallowing and breathing.		√	√
Unknown	**Inflammation of the colon (large bowel);** symptoms: diarrhea, usually with blood and mucus, stomach pain, fever		√	√

This is not a complete list of side effects. For any unexpected effects while taking Taro-Mupirocin, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature, between 15° and 25°C.
Store medicine out of the reach and sight of children.

The expiry date of Taro-Mupirocin is printed on the tube. Do not use after this date.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor:
Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario
L6T 1C1

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