PRODUCT MONOGRAPH

PrNIDAGEL®

metronidazole vaginal gel 0.75% w/w

Antibacterial Agent

Manufactured by:

Valeant Canada LP
2150 St-Elzear Blvd. West
Laval, Quebec H7L 4A8
Canada

Date of Revision:

May 28, 2020

Control No: 236355

PRODUCT MONOGRAPH

Pr Nidagel®

(metronidazole) 0.75% VAGINAL GEL

THERAPEUTIC CLASSIFICATION
Antibacterial Agent

ACTION AND CLINICAL PHARMACOLOGY

Metronidazole demonstrates antibacterial activity against bacterial classified as obligate anaerobes including *Bacteroides* and to a lesser extent against anaerobic gram-positive rods. The nitro group of the drug is thought to be reduced in the target cell leading to the production of cytotoxic metabolites.

Bioavailability studies on the administration of a single 5 gram dose of **Nidagel** (metronidazole) into the vagina of 12 normal subjects showed a mean maximum serum concentration of 237 nanograms/ml. This is approximately 2% of the mean maximum serum concentration afforded by a single 500 mg tablet of metronidazole taken orally (mean C_{MAX} = 12,785 ng/ml). Therefore, under normal usage levels, the formulation affords minimal serum concentrations of metronidazole.

INDICATIONS AND CLINICAL USE

Nidagel (metronidazole) is indicated for the treatment of bacterial vaginosis (formerly called non specific vaginitis, *Gardnerella vaginalis* or *Haemophilus* vaginitis).

A clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogenous vaginal discharge that:

a) has a pH of greater than 4.5;
b) emits a fishy amine odour when mixed with a 10% KOH solution;
c) contains clue cells on microscopic examination.

Other pathogens commonly associated with vulvovaginitis, e.g., *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Candida albicans* and herpes simplex virus should be ruled out.

Use of **Nidagel** during menses is not recommended.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Nidagel** and other antibacterial drugs, **Nidagel** 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

Nidagel (metronidazole) is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, other ingredients of the formulation or other nitroimidazole derivatives. **Nidagel** is contraindicated during the first trimester of pregnancy. (See PRECAUTIONS)

WARNINGS

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of **Nidagel** (metronidazole) therapy. **Nidagel** should be administered with caution to patients with central nervous system diseases. Psychotic reactions to oral metronidazole have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, with very rapid onset after treatment initiation, in patients with Cockayne syndrome have been reported with products containing metronidazole. In this population, **Nidagel** should therefore only be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking **Nidagel**. (See ADVERSE REACTIONS)

Susceptibility/Resistance: Prescribing **Nidagel** 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.

PRECAUTIONS

Nidagel (metronidazole) affords minimal serum levels of metronidazole compared to oral metronidazole therapy. Although these lower serum levels are less likely to produce the common reactions seen with oral metronidazole, the possibility of these are other reactions cannot be excluded.

General: Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, **Nidagel** should be administered cautiously.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with **Nidagel** and requires treatment with a candicidal agent.

No reports of alcohol interaction were received during clinical studies with **Nidagel**. Despite the relatively low serum levels of metronidazole afforded by **Nidagel**, the possibility of a disulfiram-like reaction to alcohol while on **Nidagel** therapy cannot be excluded. Patients should be advised to abstain from alcohol during therapy and for one day following therapy.

Hematologic Effects: Metronidazole is a nitroimidazole and should be used with care in patients with evidence of or history of blood dyscrasia. A mild transient leukopenia has been observed during oral metronidazole administration.

In clinical studies with 0.75% metronidazole vaginal gel a mild, clinically insignificant leukopenia was observed in some patients. Relationship to therapy could not be determined.

Drug Interactions: Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when **Nidagel** is prescribed for patients on this type of anticoagulant therapy.

Laboratory Test Interactions: Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. These determinations are based on the decrease in ultraviolet absorbance which occurs when NADH is oxidized to NAD. Metronidazole causes an increase in absorbance at the peak of NADH (340 nm) resulting in falsely decreased values.

Carcinogenicity: Metronidazole has shown evidence of carcinogenic activity following chronic oral administration in mice and rats. Pulmonary tumorigenesis has been reported in mice, and significant increases in the incidence of mammary and hepatic tumors have been found in female rats. Lifetime tumorigenicity studies in hamsters have given negative results.

These studies were conducted with orally administered metronidazole with results in significantly higher systemic blood levels than those obtained after use of 0.75% metronidazole vaginal gel.

Use in Pregnancy: There has been no experience to date with the use of **Nidagel** in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. It should not be used during the first trimester of pregnancy. Use of **Nidagel** for bacterial vaginosis in the second and third trimesters should be restricted to those patients in whom local palliative treatment has been inadequate to control symptoms. No fetotoxicity was observed after oral metronidazole in pregnant rats or mice. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See CONTRA-INDICATIONS)

Nursing Mothers: Nidagel blood levels are significantly lower than those achieved with oral metronidazole. After oral administration metronidazole has been shown to be secreted in breast milk in concentrations similar to those found in plasma. If the use of **Nidagel** is considered to be necessary in nursing mothers, the potential benefits must be weighed against the possible risks to the infant.

Use in Children: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Based on a multi-center clinical trial involving 505 patients, comparing **Nidagel** twice-daily dosing to once-daily dosing, adverse event experiences are listed below, in descending order of frequency: vaginal discharge, descriptions of which varied in both colour and consistency (12%), yeast infection (9%), vulval/vaginal irritative symptoms (9%), gastrointestinal discomfort which included patient descriptions of abdominal or stomach cramping, pain and discomfort (7%), headache (5%), nausea and vomiting (4%), pelvic discomfort (3%). The following reactions were seen at a frequency of 2%: unusual taste, dizziness, cramping, undocumented or self-diagnosed yeast infections. The following reactions were seen at a frequency of 1%: decreased appetite, diarrhea/loose stools, fatigue, medication leakage, urinary tract infection symptoms. The following reactions were seen at a frequency of <1%: abdominal bloating/gas, constipation, thirst/dry mouth, depression, irritability, menstrual discomfort, menstrual irregularities, vaginal numbness, vaginal spotting/bleeding, itching, darkened urine, Vulvovaginal burning sensation,

Other reactions noted with oral or other systemic metronidazole therapy include anorexia, epigastric distress, nausea, vomiting, furry tongue, dry mouth, metallic taste, transient eosinophilia or neutropenia, convulsive seizures, peripheral neuropathy, hearing impaired/hearing loss (including hypoacusis, deafness, deafness neurosensory), tinnitus, vertigo, incoordination, ataxia, confusion, insomnia, flushing, headache, dryness of the vagina, dysuria, darkened urine, modification of taste of alcoholic beverages, rash, pruritis, fixed drug eruption, palpitation and chest pain.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, in patients with Cockayne syndrome have been reported with products containing metronidazole. (See WARNINGS)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no human experience with overdosage of **Nidagel** (metronidazole). Massive ingestion may produce vomiting and slight disorientation. There is no specific antidote. Early gastric lavage may remove a large amount of the drug; otherwise, treatment should be symptomatic.

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

DOSAGE AND ADMINISTRATION

One applicator full (approximately 5 grams) of **Nidagel** (metronidazole) 0.75% vaginal gel should be inserted into the vagina once daily at bedtime for 5 days, or twice daily at morning and bedtime for 5 days. Controlled studies with alternate dosage schedules have not been conducted. If patients do not respond to initial therapy, it is recommended that appropriate laboratory measures be used to rule out other conditions before retreating with **Nidagel**.

Pregnant patients should not be treated during the first trimester of pregnancy. (See CONTRAINDICATIONS and PRE-CAUTIONS)

Use during menses is not recommended.

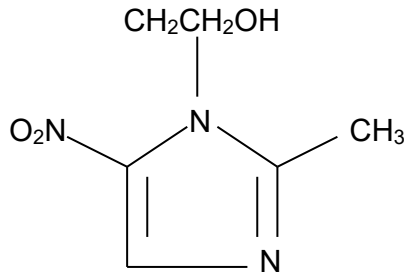
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name:
Metronidazole

Chemical Names
1*H*-Imidazole-1-ethanol, 2-methyl-5-nitro
02-Methyl-5-nitroimidazole-1-ethanol

Structural Formula:



Molecular Formula:
$C_6H_9N_3O_3$

Molecular Weight:
171.16

Description:
Metronidazole is a white to pale yellow, odorless crystal or crystalline powder with a melting point of 159°C to 163°C, and a bitter, metallic taste. It is sparingly soluble in water and alcohol. At 20°C (g/100 ml): 1.0 in water, 0.5 in ethanol. Slightly soluble in chloroform and ether (< 0.05). Soluble in dilute acids. The pH of a saturated aqueous solution is 5.8.

COMPOSITION

Nidagel is an essentially colourless to straw-coloured, slightly hazy gel. Each gram contains 7.5 mg of metronidazole. The non-medicinal ingredients are propylene glycol, carbomer 934P and edetate disodium in purified water with sodium hydroxide to adjust the pH to 4.0. Each gram contains 0.8 mg of methylparaben and 0.2 mg of propylparaben as preservatives.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15 and 25°C.

AVAILABILITY OF DOSAGE FORMS

Nidagel (0.75% metronidazole vaginal gel) is supplied in a 70 gram aluminum tube, packaged with five, 5 gram vaginal applicators.

MICROBIOLOGY

Prior names for bacterial vaginosis include non-specific vaginitis, *Haemophilus* vaginitis and *Gardnerella vaginalis* vaginitis.

Bacterial vaginosis is the clinical result of alterations in the vaginal microflora and is characterized by an abnormal quantity of both anaerobic and aerobic bacteria with anaerobes predominating. Asymptomatic infections are thought to be common. The condition generally does not cause inflammation of the vaginal epithelium. Microscopic examination of vaginal secretions normally reveals clue cells, which are epithelial cells whose borders are obscured by background bacteria and an absence of the normal flora which is predominantly composed by lactobacilli.

In women with bacterial vaginosis the concentrations of bacteria increase 100-1000 fold, and are comprised mainly of *Gardnerella vaginalis* and anaerobes. *Gardnerella vaginalis*, *Mobiluncus* species and *Mycoplasma hominis* have been implicated in bacterial vaginosis although they are present in reduced numbers in normal women, and are not always present in women with bacterial vaginosis. Large quantities of anaerobic *Bacteroides* and *Peptostreptococcus* species have been reported in bacterial vaginosis patients. It is believed that various amine by-products of anaerobic metabolism are responsible for the foul odor associated with the condition.

Lactobacilli, which always produce lactic acid, predominate in healthy women but are found in significantly lower concentrations in patients with bacterial vaginosis. It is believed that the increased alkalinity caused by the reduction of these lactobacilli somehow influences the progression of bacterial vaginosis. Bacterial vaginosis patients typically have vaginal pH elevated above 4.5 whereas normal vaginal pH is usually less than 4.5.

Metronidazole is active *in vitro* against most obligate anaerobes, but does not appear to possess clinically relevant activity against facultative anaerobes or aerobes at concentrations achievable with systemic therapy. Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimal inhibitory concentrations. Metronidazole has been shown to have *in vitro* activity against the following organisms:

Anaerobic gram-negative bacilli, including:
Bacteroides species including the Bacteroides fragilis group (B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus) and Fusobacterium species

Anaerobic gram-positive bacilli, including:
Clostridium species and susceptible strains of Eubacterium

Anaerobic gram-positive cocci, including:
Peptostreptococcus species.

Nidagel has been shown *in vivo* to have clinical activity against the following vaginal pathogens:

Gardnerella vaginalis
Bacteroides species
Mycoplasma hominis

Significant increases in vaginal lactobacilli are observed in bacterial vaginosis patients following therapy.

A summary of susceptibility data for anaerobic bacteria and Gardnerella is shown in Table 1.

TABLE 1
Susceptibility of Anaerobic Bacteria and Gardnerella to Metronidazole in Published Studies.

Organism	No. Isolates Tested	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	% Resistant @ 16 µg/mL
B. fragilis group	2693	1.0	1.0	0
Other *Bacteroides* spp.	837	2.0	4.0	7 (0.8%)
Fusobacterium	126	0.5	1.0	2 (0.8%)
Peptostreptococcus	503	1.0	>32	48 (9.5%)
Clostridium	241	1.0	8	12 (5.0%)
Other gram positive rods	61	8	>32	15 (41%)
Mobiluncus	56	16	256	17 (48%)
Gardnerella	19	8	>128	6 (32%)

PHARMACOLOGY

PHARMACOKINETICS

Two studies have been conducted with metronidazole 0.75% vaginal gel. In the first study, which utilized a randomized crossover design, the pharmacokinetics of single doses of intravaginal and oral metronidazole were compared in 12 healthy volunteers. The second study was conducted in 4 bacterial vaginosis patients. Pharmacokinetic parameters were determined after a single dose of metronidazole 0.75% vaginal gel and at steady state after 9 doses of drug. A summary of the pharmacokinetic parameters from both studies is presented in Table 2.

TABLE 2
Pharmacokinetic Parameters for Metronidazole Gel

***IN VIVO* STUDY DATA SUMMARY PARAMETERS**					
ROUTE OF ADMINISTRATION DOSAGE FORM	DOSE	C_{MAX}(%CV) (NG/ML)	T_{MAX}(%CV) (HR)	AUX(%CV) (NG-HR/ML)	COMMENTS
Intravaginal Gel	Single 5 grams Gel (37.5mg)	237(29.1)	8.37(25.9)	4977.0(53.7)	C_{MAX} and T_{MAX} determined from pharmacokinetic model fitting
Oral Tablet	500mg	898(13.5)*	1.34(46.7)	9361.6(30.7)*	C_{MAX} and T_{MAX} determined from pharmacokinetic model fitting
Intravaginal Gel	**Multiple** 5 grams Gel B.I.D X 5 days (375mg)	**Dose 1:** 214(13.1) **Dose 9:** 294(21.4)	**Dose 1:** 12** **Dose 9:** 1.53**	**Dose 1:** 1630.5(25.4) **Dose 9:** 3200.5(18.6)	C_{MAX} and T_{MAX} determined from visual observation.

*Corrected for dose difference; ** T_{MAX} reported as median value.

Vaginal absorption of the metronidazole gel formulation in patients with bacterial vaginosis is similar to that seen in normal, healthy volunteers. Cumulative metronidazole serum concentrations (steady state) in patients dosed according to the therapeutic regimen are similar to those after a single dose. The results from both studies show that minimal concentrations of metronidazole are found in the systemic circulation after single and multiple dose administration of the 0.75% intravaginal gel in normal volunteers or patients with bacterial vaginosis.

TOXICOLOGY

ACUTE TOXICITY

The acute oral LD_{50} of metronidazole as a pure substance is in the range of 3 to 5 g/kg in mice and rats, respectively.

Nidagel (metronidazole) 0.75% vaginal gel was administered in one dose at 5 g/kg by oral gavage to ten (5M, 5F) young adult Sprague Dawley rats.

No animal showed clinical signs of toxicity and no animal had visible lesions on gross necropsy. Therefore it is concluded that the oral LD_{50} of 0.75% metronidazole gel, in male and female rats, is greater than 5 g/kg of body weight.

SUBACUTE TOXICITY

Nidagel (metronidazole) 0.75% vaginal gel was administered intravaginally, 3 times per day for 21 consecutive days to female New Zealand White rabbits. Each dose was calculated to be equivalent to the human dose on a mg/kg basis.

A mild-to-moderate vaginal irritation suspected to be caused by metronidazole gel was seen in three of five animals during the study. The overall local response to metronidazole vaginal gel treatment should be classified as a mild irritation based on the fact that two of the animals in the group were almost entirely free of vaginal irritation, and that the responding animals seemed to be recovering at the time of necropsy. Correspondingly, no adverse responses in the vagina, cervix, uterus, urinary bladder, or ovaries were found upon macroscopic or microscopic examination in animals from any of the treatment groups.

CARCINOGENICITY

Metronidazole has shown evidence of carcinogenic activity following chronic, oral administration in mice and rats. Pulmonary tumorigenesis has been reported in six studies in mice. There were statistically significant increases in the incidence of hepatic tumors among female rats administered metronidazole over those noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

These studies have not been conducted with 0.75% metronidazole vaginal gel, which would result in significantly lower systemic blood levels than those obtained with oral formulations.

MUTAGENICITY

Although metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, studies in mammals (*in vivo*) have failed to demonstrate a potential for genetic damage.

REPRODUCTION AND TERATOLOGY

Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. Metronidazole administered intra-peritoneally to pregnant mice at approximately the human dose caused fetotoxicity; administered orally to pregnant mice, no fetotoxicity was observed.

PRIMARY EYE IRRITATION

Nidagel (metronidazole) 0.75% vaginal gel was placed into the everted lower lid of one eye of each of three New Zealand White rabbits. The upper and lower lids were gently held together for one second to prevent loss of material and then released. The other eye served as the untreated control. The eyes were unflushed and examined for ocular irritation at 1, 24, 48 and 72 hours after treatment. At the 72 hour reading, sodium fluorescein was used to aid in revealing possible corneal injury. Irritation was graded and scored according to the Draize technique. No pain response (vocalization) was elicited from any animal following the instillation of the test material.

Metronidazole vaginal gel 0.75% produced only very slight conjunctival irritation in one animal at the 1-hour observation. All treated eyes had returned to normal appearance by 24 hours after treatment. At 72 hours the sodium flourescein examination was negative in all animals.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrNIDAGEL®
metronidazole vaginal gel 0.75% w/w

Read this carefully before you start taking Nidagel and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Nidagel.

What is Nidagel used for?
Nidagel is a prescription medicine used to treat a bacterial infection of the vagina in adults. Antibacterial drugs like Nidagel treat **only** bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, Nidagel should be taken exactly as directed. Misuse or overuse of Nidagel could lead to the growth of bacteria that will not be killed by Nidagel (resistance). This means that Nidagel may not work for you in the future.

How does Nidagel work?
Nidagel is applied inside the vagina. It is used to kill the bacteria in the infection.

What are the ingredients in Nidagel?
Medicinal ingredient: metronidazole.
Non-medicinal ingredients: carbomer 934P, edetate disodium, methylparaben, propylene glycol, propylparaben, purified water and sodium hydroxide.

Nidagel comes in the following dosage forms:
0.75% w/w metronidazole vaginal gel, supplied in a 70 g tube, packaged with five vaginal applicators.

Do not use Nidagel if:
- You are allergic to metronidazole or any similar drug.
- You are allergic to parabens or any other ingredient of the drug (see **What are the ingredients in Nidagel**).
- You are pregnant during your first 3 months.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Nidagel. Talk about any health conditions or problems you may have, including if you:
- Have a disease of the central nervous system. Oral metronidazole has caused seizures, numbness in the fingers and toes. Contact your doctor right away if this happens.
- Have Cockayne syndrome. Some patients using metronidazole have had severe liver problems, including death, with symptoms such as:
    - Abdominal pain, nausea, vomiting.
    - Yellowing of the skin and eyes.

- Fatigue, weakness, weight loss.

Stop taking Nidagel and contact your doctor right away if this happens.

- Have liver disease with the same symptoms as above.
- Have had any blood problem. Using metronidazole has resulted in low white blood cell count (leukopenia).
- Are pregnant or plan to become pregnant. Metronidazole can be passed to the fetus and cause harm.
- Nidagel should only be used under the supervision of a doctor during the last 6 months of pregnancy.
- Are breastfeeding or planning to breastfeed.
- You have or think you have a similar infection, thrush (candidiasis) with symptoms such as:
  - Itching, pain, pain in urinating.
  - Vaginal discharge (white or watery).

  Contact your doctor right away.

Other warnings you should know about:

- Nidagel is for vaginal use only.
- Do not share your medicine.
  Avoid using Nidagel when you are having your period.
- Avoid intercourse during use of Nidagel.
- Severe liver problems, including death, were seen in patients with Cockayne syndrome using metronidazole.
- If you have Cockayne syndrome, your doctor should check your liver function many times during your treatment and after.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Nidagel:

- Warfarin and other coumarin anticoagulants.
- Certain laboratory tests results, such as: aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose.
- Alcohol may interact with Nidagel and cause some effects such as:
  - Feeling sick, vomiting, stomach pain.
  - Hot flushes, fast or uneven heartbeat.

  Avoid alcohol during Nidagel treatment and for 1 day after.

How to take Nidagel:

1. <u>Filing the applicator</u>
   - Remove cap and puncture metal seal on tube with the pointed tip of cap. (See Figure 1)
   - Screw end of applicator onto tube. (See Figure 2)
   - Slowly squeeze gel out of tube and into applicator. Plunger will stop when the applicator is full. (See Figure 3)

- Unscrew applicator and replace cap on tube.

2. Inserting the applicator
   - The applicator may be inserted while lying on your back with your knees bent or in any comfortable position.
   - Hold filled applicator by barrel, and gently insert into vagina as far as it will comfortably go. (See Figure 4)
   - Slowly press the plunger until it stops to deposit gel into vagina and then withdraw the applicator.

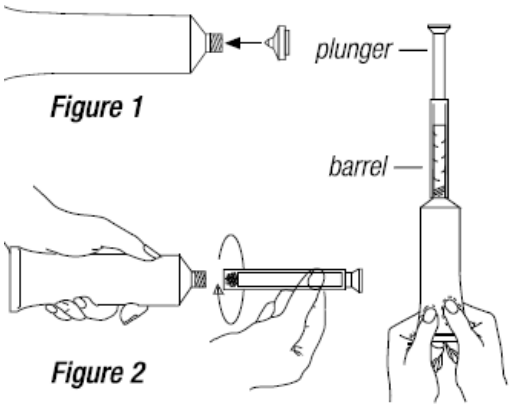

Figure 1

Figure 2

Figure 3

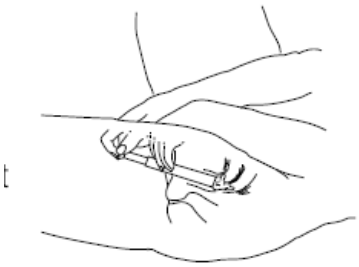

Figure 4

3. Care of the Applicator *(if prescribed twice daily)*
   - After use, pull the plunger out of the barrel. (See Figure 5)
   - Wash both plunger and barrel in warm soapy water and rinse thoroughly.
   - To reassemble applicator, gently push plunger back into barrel.

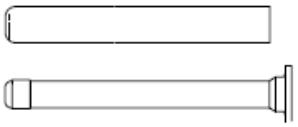

Figure 5

Usual adult dose:
One full applicator contains about 5 grams of product.
Insert one full applicator into the vagina once or twice daily, as directed by your doctor:
- Once daily at bedtime for 5 days.

- Twice daily at morning and bedtime for 5 days.

Overdose:

If you think you have used too much Nidagel, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take Nidagel, apply the product at your next scheduled time. Do not double dose.

What are possible side effects from using Nidagel?
These are not all the possible side effects you may feel when using Nidagel. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects observed with Nidagel are:
- Vaginal secretions, in different colour and texture.

Less common side effects include:
- Headache, felling sleepy or dizzy.
- Feeling sick (nausea), being sick (vomiting), loss of appetite.
- Pubic discomfort.
- Upset stomach, cramps or pain.
- Different taste in mouth, feeling thirsty, dry mouth.
- Yeast infection, urinary infection.
- Diarrhea, loose stools, bloating, gas, constipation.
- Medication leakage.
- Feeling depressed or short-tempered.
- Discomfort during period or changes in menstrual cycle.
- Vaginal loss of feeling, spotting or bleeding, itching, dark urine.

Some effects were seen with other metronidazole products. These include:
- Unpleasant feeling in tongue, metallic taste.
- Change in blood oesinophils or neutrophils.
- Seizures, nervous system problems, hearing loss.
- Loss of balance or coordination, loss of muscle control.
- Feeling confused, unable to sleep.
- Dryness of the vagina, painful urination.
- Blushing of the skin, rash, itchy skin, allergic skin reaction.
- Fast or uneven heartbeat and chest pain.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Vaginal irritation.	✓		
RARE If you suffer of Cockayne syndrome and you develop liver problems with symptoms such as stomach pain, loss of appetite, nausea, vomiting, fever, malaise, fatigue, yellowing of the skin and eyes (jaundice), dark urine, putty or mastic coloured stools or itching.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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 1908C
    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.

Storage:
Store between 15 and 25 ºC. Avoid exposure to extreme heat or cold.
See end of carton and bottom of tube for lot number and expiration date.
Keep out of reach and sight of children.

If you want more information about Nidagel:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or by contacting the manufacturer Valeant Canada LP, Laval, Quebec, H7L 4A8.

This leaflet was prepared by Valeant Canada LP.

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