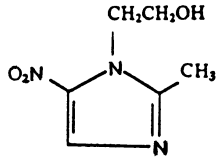
PRODUCT INFORMATION

ZIDOVAL® Vaginal Gel
(metronidazole 0.75%)

NAME OF THE MEDICINE
Metronidazole

Metronidazole is 2-methyl-5-nitroimidazole-1-ethanol. It has a chemical formula of $C_6H_9N_3O_3$, a molecular weight of 171.16, and the following structure:



CAS No: 443-48-1

DESCRIPTION
Zidoval Vaginal Gel is an intravaginal dosage form of the synthetic antibacterial agent, metronidazole. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an anti-bacterial agent.

Zidoval Vaginal Gel is a non-sterile gelled, purified water solution, containing metronidazole at a concentration of 7.5 mg/g (0.75%). The gel is formulated at the normal vaginal pH of 4.0. The gel also contains carbomer 974P, disodium edetate, methylhydroxybenzoate, propylhydroxybenzoate and propylene glycol. Each 5 g applicator of vaginal gel contains approximately 37.5 mg of metronidazole. Zidoval Vaginal Gel does not contain mineral oil.

PHARMACOLOGY
Microbiology
Metronidazole is a synthetic agent, which is effective against a wide range of obligate anaerobes. It is not effective against aerobes or facultative anaerobes. Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimum inhibitory concentration. The antibacterial activity results from the disruption of DNA and the inhibition of nucleic acid synthesis.

The aetiology of bacterial vaginosis is unclear and changes in vaginal flora which accompany bacterial vaginosis are probably its manifestation rather than its cause. Monitoring changes in vaginal flora by Gram stain slides of vaginal discharge smears may supplement diagnosis and assessment of treatment efficacy by standard clinical criteria.

Metronidazole has been shown to have *in-vivo* and clinical activity against:

- Obligate anaerobic gram negative bacilli including *Bacteroides* species *(B. fragilis, B. distasonis, B. ocatus, B. thetaiotaomicron, B. vulgaris)* and *Fusobacterium* species.
- Anaerobic gram positive bacilli including *Clostridium* species and susceptible strains of *Eubacterium.*
- Anaerobic gram-positive cocci including *Peptostreptococcus* species.

Treatment success in bacterial vaginosis may be accompanied by a decrease in (but not elimination of) organism such as *Gardnerella* vaginalis and *Bacterioides* species. This may also be accompanied by an increase in *Lactobacillus* species in the vagina.

Pharmacokinetics

Healthy Volunteers: Following a single, intravaginal 5 g dose of Zidoval Vaginal Gel 0.75% (equivalent to 37.5 mg of metronidazole) administered to 12 healthy volunteers, a mean maximum serum metronidazole concentration of 237 ng/mL was achieved (range: 152 to 368 ng/mL). This is approximately 2% of the mean maximum serum metronidazole concentration achieved in the same subjects administered a single, oral 500 mg dose of metronidazole (mean C_{max} = 12,785 ng/mL, range: 10,013 to 17,400 ng/mL). These peak concentrations were obtained between 6 to 12 hours after dosing with Zidoval Vaginal Gel and 1 to 3 hours after dosing with oral metronidazole.

The extent of exposure (area under the curve [AUC]) of metronidazole, when administered as a single intravaginal 5g dose of Zidoval Vaginal Gel, was approximately 4% (4,977 ng/hr/mL) of the AUC of a single oral 500 mg dose of metronidazole (approximately 13,3395 ng/hr/mL). Dose-adjusted comparisons of AUCs indicated that the absorption of metronidazole administered vaginally was approximately half that of an equivalent oral dosage on a milligram-per-milligram comparison basis.

Patients With Bacterial Vaginosis: Following administration of 5 g doses of Zidoval Vaginal Gel twice daily for 5 days to 4 patients with bacterial vaginosis, mean maximum serum metronidazole concentrations of 214 ng/mL on day 1 and 294 ng/mL (range: 228 to 349 ng/mL) on day 5 (steady-state) were achieved. Steady-state metronidazole serum concentrations following oral dosages of 400 to 500 mg twice daily have been reported to range from 6,000 to 20,000 ng/mL.

CLINICAL TRIALS

Four randomised, double-blind, controlled clinical studies demonstrated the effectiveness and safety of Zidoval Vaginal Gel in the treatment of bacterial vaginosis. The bases for clinical diagnosis of bacterial vaginosis in these studies were the presence of ≥20% clue cells in vaginal discharge and 2 of the following 3 clinical criteria: i) homogenous vaginal discharge; ii) a vaginal discharge with a pH≥4.7; iii) a vaginal discharge emitting a positive amine odour test. In addition, Gram stains were also used to confirm accuracy of diagnosis in these studies. Patients were considered as treatment success if all 3 clinical criteria were absent and clue cells, if present, must be <20%.

In a randomised, double-blind, placebo-controlled clinical trial, Zidoval Vaginal Gel (5 g) given intravaginally twice daily for five days for treatment of bacterial vaginosis (assessed by Amsel Criteria) achieved treatment success (81%; n=43) at 12-16 days post-therapy that was statistically significantly greater than the placebo (11%; n=35). At follow-up visit (28-32 days post-therapy), treatment success for Zidoval Vaginal Gel (76%; n=38) remained statistically significantly greater than the placebo (6%; n=34). Results of Gram stain scores agreed with clinical diagnosis overall in 90% cases at all visits combined.

In a randomised, investigator blinded, parallel clinical trial, Zidoval Vaginal Gel (5 g) given intravaginally twice daily for five days for treatment of bacterial vaginosis achieved comparable treatment successes (86%, n=37, at 2 weeks post initiation of therapy; 71%, n=34, at 4 weeks post initiation of therapy) to oral 500 mg metronidazole tablets given twice daily for 7 days (84%, n=44, at 2 weeks post initiation of therapy; 68%, n=41, at 4 weeks post initiation of therapy). Clinical and Gram stain diagnoses were in agreement 90% of the time.

In a randomised, double-blind clinical trial, Zidoval Vaginal Gel (5 g) given intravaginally twice daily for five days for treatment of bacterial vaginosis achieved comparable (p=0.333) treatment success (79%, n=103) at 12-16 days post-therapy to Sultrin (sulfathiazole, sulfacetamide, sulfabenzamide) cream given twice daily intravaginally for 5 days (71%, n=113). At follow-up visit (28-32 days post-therapy), treatment success for Zidoval Vaginal Gel (66%, n=96) was statistically significantly greater (p=0.018) than Sultrin (47%, n=109). Results of Gram stain scores agreed with clinical diagnosis overall in 89% cases in Zidoval group and in 87% in Sultrin group.

In a randomised, investigator blind clinical trial, the efficacy of Zidoval Vaginal Gel (5 g) given intravaginally twice daily versus once daily for five days for treatment of bacterial vaginosis was compared. At visit 2 (7-12 days post-therapy) and visit 3 (28-35 days post-therapy) respectively, 77% (n=199) and 58% (n=180) of patients were considered treatment success in the once daily dosing group. For the twice daily dosing regimen, corresponding treatment success rates were 80% (n=196) and 61% (n=178), respectively. Difference between treatment groups was not statistically significant. Gram stain scores and clinical diagnosis correlated in 83% cases.

INDICATIONS

Zidoval Vaginal Gel 0.75% is indicated in the treatment of symptomatic bacterial vaginosis (formerly referred to as *Haemophilus vaginalis* vaginitis, *Gardnerella vaginalis* vaginitis, non-specific vaginitis, *Corynebacterium vaginale* vaginitis or anaerobic vaginosis).

Note: For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of at least three of the following four criteria:
a) a vaginal discharge pH of greater than 4.5;
b) a vaginal discharge emitting a "fishy" amine odor when mixed with a 10% KOH solution;
c) a vaginal discharge containing clue cells on wet mount microscopy examination;
d) a gram stain consistent with a diagnosis of bacterial vaginosis (*Lactobacillus morphotype* absent or markedly decreased, *Gardnerella morphotype* predominant flora, white blood cells absent or few, *Mobiluncus morphotype* may or may not be present).

A diagnosis of bacterial vaginosis requires that other pathogens which may be associated with genital infection, such as *Trichomonas vaginalis, Candida albicans, Chlamydia trachomatis and Neisseria gonorrhoeae,* should be ruled out by appropriate laboratory means.

CONTRAINDICATIONS

Zidoval Vaginal Gel is contraindicated for patients with a prior history of hypersensitivity to metronidazole, hydroxybenzoates, other ingredients of the formulation or other nitroimidazole derivatives.

PRECAUTIONS

General:

Approximately 6-10% of patients treated with Zidoval Vaginal Gel developed symptomatic *Candida* vaginitis during or immediately after therapy. This may be due to known or previously unrecognised vulvovaginal candidiasis may present with more prominent symptoms during therapy. Zidoval Vaginal Gel contains ingredients that may cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

Convulsive Seizures and Peripheral Neuropathy
Some patients treated with oral or intravenous metronidazole have been reported to have convulsive seizures or peripheral neuropathy, the latter characterised mainly by numbness or paraesthesia of an extremity. While the occurrence of serious neurological symptoms with Zidoval Vaginal Gel is unlikely, the appearance of abnormal neurological signs should prompt discontinuation of therapy. Zidoval Vaginal Gel should be administered with caution to patients with central nervous system diseases.

Cockayne Syndrome
Cases of severe hepatotoxicity or 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 for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and 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 medicine should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report symptoms of potential liver injury to their physician and stop taking metronidazole.

Haematologic Effects
Some patients treated with oral metronidazole have been observed to have a mild transient leukopenia. Zidoval Vaginal Gel should be administered with caution to patients with evidence of or a history of blood dyscrasia.

Patients with Hepatic Impairment
Patients with severe hepatic disease metabolise metronidazole slowly. This may result in the accumulation of metronidazole and its metabolites in the plasma. Zidoval Vaginal Gel should be administered with caution in patients with evidence of hepatic dysfunction. However, a total treatment course of 187.5 mg is unlikely to lead to excessive serum levels.

Patients with Renal Impairment
In patients with renal failure, there is no accumulation of metronidazole however hydroxy and acid metabolites are retained. Haemodialysis removes metronidazole and these metabolites.

Use in Pregnancy (*Category B2)*
The potential adverse effects of Zidoval Vaginal Gel on pregnancy have not been determined. Metronidazole crosses the placental barrier and enters the foetal circulation rapidly. Metronidazole blood levels are significantly lower after administration of Zidoval Vaginal Gel than those achieved with oral metronidazole.

A substantial amount of data is available regarding the effects of human exposure to metronidazole in pregnancy over more than 30 years. A review of literature reports in 1469 women treated with metronidazole during pregnancy, 206 during the first trimester, concluded that the incidence of abortions, perinatal death and malformations, or of icterus neonatorum was not increased. A decade later, another literature review was published on 2139 women (254 treated with metronidazole during first trimester, 521 during second trimester, 554 during third trimester and 880 at an unspecified time during pregnancy) concluded that metronidazole was safe during pregnancy.

In 7 retrospective studies in UK and USA, the effect of metronidazole use was examined in 1776 pregnancies; in 246 pregnancies the drug was used during first trimester. Dosage regimens varied; oral dose of 250-750 mg/day for 7-10 days either alone or in combination with 500 mg vaginal suppository. No evidence of increase in the incidence of any particular abnormality was seen in these studies. Collectively, these studies led to the conclusion that metronidazole was safe to use during pregnancy, including during the first trimester.

In two prescription-event studies, 2327 women who had a prescription for metronidazole filled at any time during pregnancy did not show an increase in the incidence of malformations in babies born to them.

A meta-analysis of 7 studies (1336 patients exposed; 154,163 patients with no exposure to the drug) showed no evidence of increased risk of malformation from the use of metronidazole during pregnancy. A similar analysis from 5 studies (2524 patients exposed and 196,927 not exposed to drug) showed no relationship between metronidazole use during pregnancy and birth defects.

In a prospective follow-up of 34 cases exposed to metronidazole during pregnancy, metronidazole was not considered to cause birth defects. Twenty five cases had received the drug during first trimester, seven during the second and one during the third trimester and date of exposure for one was not known.

Although no conclusive evidence of foetotoxicity or teratogenicity has been observed in animal studies with other forms of metronidazole, and clinical experience to date with the use of metronidazole in pregnant women has revealed no evidence of a foetotoxic or teratogenic effect of the drug, there are no adequate and well-controlled studies of therapy with Zidoval Vaginal Gel in pregnant women.

Intravenous and oral formulations of metronidazole are not recommended to be given in the first trimester of pregnancy because it crosses the placenta and enters the foetal circulation rapidly. Although it has not been shown to be teratogenic in either human or animal studies, such a possibility can not be excluded. Metronidazole vaginal gel should be used in pregnancy if no other treatment option is considered appropriate.

Use in Lactation
After oral administration, metronidazole has been shown to be secreted in breast milk in concentrations similar to those found in plasma. Metronidazole plasma levels are significantly lower after administration of Zidoval Vaginal Gel than those achieved with oral metronidazole. Since the potential adverse effects of metronidazole on postnatal development have not been determined, thus a decision should be made, whether to discontinue breast-feeding or treatment with Zidoval Vaginal Gel, taking into account the importance of the treatment to the mother.

Use in Children
The safety and efficacy of Zidoval Vaginal Gel in children have not been established.

Genotoxicity and Carcinogenicity
Although metronidazole has shown mutagenic activity in several *in vitro* systems, including bacteria, there is no conclusive evidence of genotoxicity in mammals. Chronic oral administration of metronidazole showed increased tumour incidence in rats and mice. The results of rodent tests are not always indicative of human risk, in part, due to metabolic and digestive differences. While the results of genotoxicity, mutagenicity, and carcinogenicity assays of metronidazole in rodent-based systems and in vitro are equivocal, the human use of

metronidazole as a therapeutic agent since 1960 shows no conclusive evidence of human genotoxicity, mutagenicity, and carcinogenicity at therapeutic levels of metronidazole. Retrospective studies in women treated systemically with metronidazole have revealed no increased incidence of tumour formation compared to the untreated population.

Effect on Laboratory Tests
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 glucose hexokinase. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation reduction of nicotinamide adenine dinucleotides (NAD+NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

INTERACTIONS WITH OTHER MEDICINES
Zidoval Vaginal Gel therapy results in markedly lower serum levels of metronidazole when compared to oral metronidazole therapy. Although these lower serum levels are less likely to result in the interactions that have been observed with oral metronidazole, the possibility of these interactions can not be excluded.

Alcohol: Concurrent usage of oral metronidazole and alcohol may result in a disulfiram-like reaction. Despite the relatively low serum levels of metronidazole produced following administration of Zidoval Vaginal Gel, the possibility of a disulfiram-like reaction to alcohol while on Zidoval therapy can not be excluded. Patients should be cautioned about drinking alcohol while being treated with Zidoval Vaginal Gel.

Carmustine (BCNU) or cyclophosphamide: Metronidazole should be used with caution in patients receiving these drugs.

Coumarin Anticoagulants: Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. Zidoval Vaginal Gel should be administered with caution in patients on this type of anticoagulant therapy.

Cyclosporin and 5-Fluorouracil: Oral metronidazole has been shown to increase the plasma concentrations of cyclosporin and 5-fluorouracil. Although, vaginal administration of metronidazole results in markedly lower plasma metronidazole concentrations when compared to oral metronidazole, the possibility of these interactions can not be ruled out.

Disulfiram: Concurrent usage of oral metronidazole and disulfiram have been reported to cause psychotic reactions in alcoholic patients. Zidoval Vaginal Gel should not be administered to patients who have taken disulfiram within the past 2 weeks.

Lithium: Short-term oral metronidazole therapy in patients stabilised on relatively high doses of lithium has been associated with elevation of serum lithium levels and, in a few cases, signs of lithium toxicity.

ADVERSE EFFECTS

Clinical Trial Data

In four randomised placebo- or active-controlled pivotal clinical trials, adverse events reported by the investigator as probably or possibly related to treatment and with an incidence of 1% or greater are presented in the table below. A dash represents an incidence of less than 1%.

	Zidoval Vaginal Gel	Placebo Vaginal Gel	Metronidazole Oral Tablets	Sultrin Vaginal Cream
Dosing regimen	Od or bd for 5 days	bd for 5 days	500 mg bd for 7 days	bd for 5 days
	N=720	N=46	N=50	N=121
Skin and Appendages				
Allergic Reaction	-	-	2.0%	-
Gastrointestinal				
Gastrointestinal Discomfort	4.7%	-	-	-
Nausea	-	-	18.0%	3.3%
Nausea and Vomiting	2.2%	-	-	-
Unpleasant Taste/Feeling on Tongue	2.1%	2.2%	40.0%	-
Diarrhoea	-	-	10.0%	2.5%
Decreased Appetite	1.1%	-	6.0%	-
Constipation	-	-	12.0%	-
Abdominal Cramping	-	-	12.0%	-
Metallic Taste in Mouth	-	-	-	1.7%
Reproductive				
Yeast Infection	8.6%	-	22.0%	1.6%
Vaginal Discharge	8.2%	-	2.0%	-
Vulva/Vaginal Irritative Symptoms	6.1%	-	-	-
Itching, Vaginal and Perianal	-	2.2%	-	-
Vulvar Burning	-	2.2%	-	-
Vulvar Lesions	-	2.2%	-	-
Vaginal Itching	-	-	10.0%	-
Vaginal Burning	-	2.2%	-	2.5%
Pelvic Discomfort	1.9%	-	-	-
Urinary				
Darkened Urine	-	-	20.0%	-
Neurologic				
Dizziness	1.7%	-	10.0%	-
Headache	2.1%	-	4.0%	-
Other				
Fatigue	-	-	2.0%	-
Trouble Sleeping	-	-	6.0%	-
Cramping: Uterine/Menstrual/Vaginal	-	-	-	3.3%

Post-Marketing Data
The listing below includes all spontaneous adverse events, reported worldwide during the period of August 1992 to December 1997, and is presented at frequency of:
Very Common ≥1/10
Common ≥ 1/100 and <1/10
Uncommon ≥ 1/1000 and <1/100
Rare ≥ 1/10,000 and <1/1000
Very Rare <1/10,000

Application Site Disorder: *Very rare*: application site reaction
Body as a Whole: *Very rare*: allergic reaction
Central and Peripheral Nervous System Disorders: *Very rare*: dizziness, headache, paraesthesia
Gastrointestinal System Disorders: *Very rare*: abdominal pain, diarrhoea, nausea
Reproductive Disorders, Female: *Very rare*: leukorrhoea, vaginitis, vulvar disorder
Skin and Appendages Disorder: *Very rare*: pruritus genital, rash, urticaria.
Special Senses Other, Disorder: *Very rare*: taste perversion.

DOSAGE AND ADMINISTRATION
The recommended dose is one applicator full of Zidoval Vaginal Gel (approximately 5 g containing approximately 37.5 mg of metronidazole) intravaginally once a day, at bedtime, for 5 days.

OVERDOSAGE
There is no human experience with overdosage of Zidoval Vaginal Gel.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia)

PRESENTATION AND STORAGE CONDITIONS
Each 5 g of Zidoval Vaginal Gel 0.75% contains 37.5 mg of metronidazole. Zidoval Vaginal Gel is supplied in a 40 g tube and packaged with 5 disposable applicators.
Store below 25ºC.
Do not freeze.

NAME AND ADDRESS OF THE SPONSOR
iNova Pharmaceuticals (Australia) Pty Limited
Level 10, 12 Help Street,
Chatswood, NSW 2067

POISON SCHEDULE OF THE MEDICINE
S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)
28 March 2000

DATE OF MOST RECENT AMENDMENT
21 March 2017