

PRODUCT MONOGRAPH

Prevegyn[®]

Vitamin C (ascorbic acid) 250 mg controlled-release vaginal tablets

Gynecological antiinfectives and antiseptics (G01AD03 Ascorbic Acid)

(NPN 80038565)

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Prevegyne®

Vitamin C (ascorbic acid)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Vaginal	Tablet / 250 mg	Lactose monohydrate <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.</i>

INDICATIONS AND CLINICAL USE

Prevegyne® helps to reduce/relieve symptoms of non-specific vaginitis/bacterial vaginosis.

CONTRAINDICATIONS

- Patients who are hypersensitive to ascorbic acid or to any ingredient in the formulation. For a complete listing of nonmedicinal ingredients, see **DOSAGE FORMS, COMPOSITION AND PACKAGING.**

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Many mutagenicity studies were conducted on ascorbic acid [1]. On the whole, the weight of evidence indicates that ascorbic acid does not produce gene mutation in *Salmonella typhimurium* nor in mammalian cells using the mouse lymphoma assay [2,3]. Positive results were consistently obtained in *in vitro* assays for Sister-Chromatid Exchanges (SCE) and Unscheduled DNA Synthesis (UDS) induction, indicating the ability to produce DNA damage under certain conditions [4,5]. Negative results were obtained in *in vivo* assays, using high dose levels, for the induction of micronuclei and SCEs in bone marrow [6].

Two year carcinogenicity studies were performed in mice and rats in the context of the USA National Toxicology Program. The animals received diets containing 0, 25,000 and 50,000 ppm of ascorbic acid in three different groups. Under the conditions of this bioassay, ascorbic acid was not carcinogenic in male and female rats and mice [7].

Genitourinary

Although not conclusive, there were some cases where infection due to *Candida* was intensified by a vaginal acidification following ascorbic acid treatment [19].

Hematologic

There have been rare reports of ascorbic acid interfering with the effectiveness of anticoagulant medications like warfarin (Coumadin[®]) [8].

Although vaginally applied ascorbic acid does not enter the systemic circulation in significant amounts, oral administration of ascorbic acid is known to enhance the availability and absorption of iron from nonheme iron sources [9] as a result ascorbic acid may be contraindicated in patients with hemolytic anemia.

Hepatic/Biliary/Pancreatic

After oral administration, ascorbic acid easily reaches the tissues. Plasma protein binding is around 25% [10]. Ascorbic acid accumulates in adrenal and pituitary glands [11]. The liver, spleen, brain and the optic lens contain appreciable concentrations of that vitamin. Ascorbic acid is excreted in the urine over a period of 10 days [11].

Ophthalmologic

Ascorbic acid was found to be non-irritating to the eye in animal studies [12].

Renal

Ascorbic acid is reversibly oxidized to L-dehydroascorbic acid and partially metabolized to inactive sulphide and oxalic acid, which are expelled in urine [10]. Only in excessive state is significant oxalate found in the urine, which accounts for one of the few potential clinical toxicities of systemic vitamin C supplementation, oxalic acid renal stones. Although vaginally applied ascorbic acid does not enter the systemic circulation in significant amounts, oral administration of ascorbic acid may be contraindicated in patients with past history of renal calculi [13].

Sexual Function/Reproduction

Due to the particular indications of Prevegyn[®], the reproductive and developmental toxicity studies of ascorbic acid are very important. The vitamin appeared devoid of adverse effects on reproduction parameters even at doses that are more than two orders of magnitude higher than those contained in Prevegyn[®] [14].

Skin

Ascorbic acid was found to be non-irritating to the skin in animal studies [15].

Special Populations

Pregnant Women:

Prevegyn[®] should not be used during pregnancy.

A clinical study on 54 pregnant women was conducted with Vagi-C (Prevegyn[®]). No special adverse events were detected during pregnancy. No complications were reported in the pregnancy outcomes [16,17].

Nursing Women:

Prevegyn[®] should not be used during nursing/breastfeeding.

Use in breastfeeding has not been studied.

Ascorbic acid is present in breast milk after oral administration [18]. However, vaginally applied ascorbic acid does not enter the systemic circulation in significant amounts.

Monitoring and Laboratory Tests

No clinically relevant changes on routine laboratory tests were seen after vaginal treatment with 250 mg ascorbic acid for 6 days [19].

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions associated with Prevegyne[®] are pruritus (itching) and burning. Other adverse reactions associated with Prevegyne[®] may include leucorrhoea (vaginal discharge), pain or insomnia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Polatti et al. 2006 – A randomized, double-blind, controlled study evaluated the safety of 3 different formulations of a vaginal tablet each containing 250 mg ascorbic acid [20]. Thirty-nine women with vaginal pH ≥ 5 , without evidence of vaginal infections, were randomly assigned to groups of 13 patients to receive 1 of the 3 formulations. The patients were instructed to introduce one (1) vaginal tablet once a day at bedtime for six (6) consecutive days. Four (4) patients were lost to follow-up.

Overall, 16 adverse events were reported by 14 subjects (40%). Vaginal itching and burning (14.3%) were the most frequently reported adverse events; the relationship with the product application was rated as possible in all cases. One (1) suffered from candidiasis and had to take a specific therapy. Leucorrhoea (thick, whitish vaginal discharge) was reported in four (4) cases (11.4%). Moderate edema was reported in one (1) patient (2.8%), who complained also of burning. The relative and absolute frequency rate of occurrence of adverse events in the three groups showed no clinically relevant differences among groups.

Petersen and Magnani 2004 – A randomized, double-blind, placebo-controlled clinical study evaluated the safety and tolerability of the vaginal 250 mg-ascorbic acid formulation given once a day in patients suffering from bacterial vaginosis [19]. The total length of the study was 20 days, including a treatment phase of six (6) days.

Adverse events occurred in four (4) patients. Two (2) patients in the active group showed *Candida* superinfections and two (2) patients in the placebo group reported pruritus and cystitis, respectively.

Petersen 1998 – A double-blind, randomized, placebo-controlled, multicenter clinical study evaluated the safety of vaginal applied ascorbic acid (Vagi-C/Prevegyne[®]) in the treatment of bacterial vaginosis [16]. Thirty out of 277 women (11.1%) were pregnant. One tablet was applied once a day for 6 days.

Adverse events were reported by 12 (8.8%) patients from the placebo group and 15 (10.6%) patients from the ascorbic acid group. Events reported among the patients from the ascorbic acid group were as follows: pruritus (itching), burning, pain, leucorrhoea (vaginal discharge) and insomnia.

Petersen 1999 – A non controlled, non randomized study with 24 pregnant women evaluated the safety of ascorbic acid vaginal tablets (250 mg) given once daily to prevent preterm delivery and abortions [17]. Twenty-four pregnant women considered of high risk to suffer from bacterial vaginosis and therefore preterm delivery and abortions were treated with Vagi-C (Prevegyne®) once per day during several weeks [17]. Nineteen women had a healthy baby without any developmental complications, and 18 of these babies were born in week 34. Only in one case with an apparent cervicitis resistant to antibiotics, a late abortion appeared in the 22nd week of gestation. Four women had not given birth when the study report was written. No adverse events were reported.

No death, serious or significant adverse events occurred during the above four (4) clinical trials.

Table 1 - Incidence of Adverse Events in Individual Studies

Body System/ Adverse Event	Polatti <i>et al.</i> 2006	Petersen and Magnani 2004		Petersen 1998		Petersen 1999
	Vagi-C** (Prevegyne) n= 35 (%)	Vagi-C** (Prevegyne) n= 50 (%)	Placebo n= 50 (%)	Vagi-C** (Prevegyne) n= 141 (%)	Placebo n= 136 (%)	Vagi-C** (Prevegyne) n= 24 (%)
Reproductive System and Breast Disorders						
Genital Discharge	4			1	1	
General Disorders and Administration Site Conditions						
Edema	1					
Pain				3	1	
Skin and Subcutaneous Tissue Disorders						
Pruritus	5	*	*	7	7	
Nervous System Disorders						
Burning Sensation	5			5	3	
Infections and Infestations						
Candidiasis	1	2				
Psychiatric Disorders						
Insomnia				1		

* Pruritus was reported in few patients in both groups at each visit, without any clinical or statistical difference between the active treatment and placebo.

**Vagi-C and Prevegyne® are identical in formulation.

Abnormal Hematologic and Clinical Chemistry Findings

None reported.

Post-Market Adverse Drug Reactions

Aggregate case reports summary of non-serious reactions are presented in Table 2 from August 18, 2010 to October 31, 2012. Reactions are presented by MedDRA System Organ Class (SOC) and Preferred Terms (signs, symptoms and diagnosis) from spontaneous notification. A total of sixty-seven (67) ADRs were received or documented during this period. Adverse reaction reports are suspected associations between the health product and the reaction and do not necessarily infer causality. No serious adverse reaction was reported during this period.

Table 2 - Cumulative Summary of Post-Marketing Adverse Reactions

System Organ Class/ MedDRA Preferred Terms version 15.1	Reported to Duchesnay	Reported to Health Authority
Cardiac		
Palpitations	1	0
Gastrointestinal disorders		
Abdominal bloating	1	0
Abdominal pain	2	0
General disorders and administration site conditions		
Mucosal eruption	1	0
Pain	9	0
Psychiatric conditions		
Insomnia	1	0
Reproductive system and breast disorders		
Genital burning sensation	6	0
Menstruation delayed	1	0
Vaginal discharge	10	0
Vaginal exfoliation	1	0
Vaginal haemorrhage	5	0
Vulval oedema	2	0
Vulvovaginal burning sensation	13	1
Vulvovaginal discomfort	4	0
Vulvovaginal pruritus	7	0
Skin and subcutaneous tissue disorders		
Erythema	1	0
Pruritus	1	0

DRUG INTERACTIONS

Overview

Vaginal applied ascorbic acid does not enter the systemic circulation in significant amounts. No drug interactions have been reported specifically with vaginal use. However, some of the most important pharmacokinetic interactions of ascorbic acid after oral administration are shown in Table 3. Ascorbic acid solutions should not be mixed with salts of metals, especially copper and iron and oxidizers [10]. Oral administration of ascorbic acid increased the rate of elimination of amphetamine and tricyclic antidepressants. It destroys vitamin B₁₂ and increases the concentration of sodium (Na⁺) and uric acid in blood. High serum levels of ascorbic acid can falsify the results of some clinical tests.

Drug-Drug Interactions

No drug interactions have been reported with the intravaginal use of Prevegyne[®]. Some of the most important pharmacokinetic interactions reported after oral administration of ascorbic acid are shown in Table 3.

Table 3 - Established or Potential Drug-Drug Interactions with Ascorbic Acid (Vitamin C) after Oral Administration

Proper name	Effect	Clinical comment
Aspirin and other anti-inflammatory drugs, or oral contraceptives	Reduce	Salicylates stimulate ascorbic excretion; more ascorbic acid is needed [8]
Warfarin (Coumadin [®]) or heparin	Reduce	High-dose ascorbic acid might reduce their effectiveness [8]
Iron supplements	Enhance	High-dose ascorbic acid can cause the patient to absorb too much iron. This is especially a problem for people with diseases that cause them to store too much iron [9]
Medications in the nitrate family	Additive	Ascorbic acid may help to maintain their effectiveness [21,22]
Protease inhibitors for HIV	Reduce	High-dose ascorbic acid may reduce their effectiveness [23]
Cancer chemotherapy	Reduce	Do not use ascorbic acid except on physician's advice [24]

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

No clinically relevant changes on routine laboratory tests were seen after vaginal treatment with 250 mg ascorbic acid for 6 days [19]. However, following oral administration, ascorbic acid may alter the determination of urine glucose, lactate dehydrogenase, serum transaminase and serum bilirubin [8,9].

DOSAGE AND ADMINISTRATION

Dosing Considerations

Recommended Dose and Dosage Adjustment

The recommended standard dosage is one (1) vaginal tablet of 250 mg per day (in the evening). The duration of treatment is for 6 days in cases of light to moderate bacterial infection. A healthcare professional may prolong treatment beyond 6 days.

Missed Dose

In the event that a dose is missed, it should be inserted as soon as possible. Regular schedule can be resumed the following day. It is important that only one (1) Prevegyne[®] tablet be inserted daily or within a 24-hour period. Therefore, dose should not be doubled nor two (2) tablets be inserted at once to catch-up the missed dose.

Administration

The patient is to wash her hands. One (1) Prevegyne[®] tablet is to be inserted deeply into the vagina using the index and/or middle finger. To ease insertion it is recommended to insert the tablet in a lying position, preferably at bedtime. Prevegyne[®] tablets are a special vaginal galenic formulation capable of slowly releasing moderate amounts of ascorbic acid over hours. Prevegyne[®] tablets should not be crushed or intentionally split. In order to decrease the risk of tablet breaking, a localized pressure should be applied at the edge of the blister (direct pressure in the center of the tablet should be avoided). The tip of a spoon or a fingernail may be used to gently break the foil underneath the blister.

OVERDOSAGE

Vaginally applied ascorbic acid does not enter the systemic circulation in significant amounts. Only one (1) tablet should be inserted vaginally per day.

ACTION AND CLINICAL PHARMACOLOGY

Ascorbic acid is readily absorbed from the intestine via an energy-dependent process that is saturable and dose-dependent. The mechanism of intestinal absorption has been extensively characterized in *in vitro* and *in vivo* models, in particular in the guinea-pig. The kinetic behaviour of ascorbic acid has been characterized: after an oral administration of the ¹⁴C vitamin to guinea pigs, the radioactivity peak in plasma was reached in 1.5 h and terminal half life was 61 h. Ascorbic acid seemed to be bound in several tissues (adrenals, testes) to a higher percentage than in plasma. By day 9 from administration, 63% of the radioactivity had been exhaled with respiratory CO₂, while only 7 % and 3 % were excreted with the urine and feces, respectively. With regards to urinary metabolites, most of the excreted label was incorporated in oxalate, while unchanged ascorbic acid, dehydroascorbic acid and 2,3-diketogulonic acid accounted for about 2-3% of the given dose.

Mechanism of Action

The mechanism of action of vaginally applied ascorbic acid is based on acidification of the vaginal fluid [16,17,19,20]. Decreased vaginal pH is detrimental for the survival of pathogenetic microorganisms, but not for *Lactobacillus acidophilus* that is responsible for the acidic vaginal pH and defends the host against pathogen colonization. Therefore, the vaginal application of ascorbic acid (250 mg) in the form of silicone-coated ascorbic acid tablets [19] ensures a long-lasting normalization of the vaginal flora. The special galenic formulation of this product guarantees efficient and controlled ascorbic acid release over hours, thereby reducing the risk of significant irritation of the vaginal epithelium due to too high local ascorbic acid concentrations [16,17,19,20].

Pharmacokinetics

The pharmacokinetics of ascorbic acid has been explored by numerous nonclinical and clinical studies and the absorption, distribution, metabolism and excretion are known quite well, when this substance is administered by the intravenous and the oral route. However, it must be considered that Prevegyne[®] contains 250 mg of vitamin C used vaginally. Even in the hypothesis of a very high bioavailability of the vaginally administered ascorbic acid, this would not appear to pose any threat to the patient, since higher oral doses (doses up to 6,000 mg per day) have been administered for long periods of time in the absence of severe adverse effects. The maximum recommended dose for ascorbic acid is 2,000 mg per day for adults [25]. This is based on the Tolerable Upper Intake Level which applies to total vitamin C (ascorbic acid) intake from food and supplements [26].

Absorption and bioavailability: The vaginal application of ascorbic acid (250 mg) in the form of silicone-coated ascorbic acid tablets ensures the local release of the vitamin over hours at efficient concentrations [19]. At the same time, too high local ascorbic acid concentrations are prevented. In addition, vaginally applied ascorbic acid does not enter the systemic circulation in significant amounts and therefore is significantly below the maximum recommended doses of daily intake in humans.

The dermal penetration and degradation of ascorbic acid after topical application of an 8% vitamin formulation with a pH of 3.1 was investigated *ex vivo* on human skin fragments [27]. Ascorbic acid and its metabolites were collected by microdialysis and assessed by gas chromatography mass spectrometry [27]. The results of this study concluded that in spite of its low lipophilicity, ascorbic acid penetrates the skin rapidly after topical application. Topical application of ascorbic acid enhances its steady-state dermal levels reaching 8.5 times the normal tissue value during 8 h [27]. After this period, dermal concentrations decrease to the basal level. Although ascorbic acid is a very hydrophilic compound with a partition coefficient between octanol and water of 0.02 ± 0.002 , several scientists have confirmed the skin permeation of ascorbic acid [27]. No degradation of ascorbic acid was detected. Ascorbic acid remained stable and metabolites were not formed [27]. The diffusivity determined from the lag time was approximately 1,000 times higher in the stripped skin, compared with whole skin. There was a dramatic increase in the permeation rate in stripped skin indicating that the major barrier to the skin permeation of ascorbic acid is the stratum corneum.

Based on *in vitro* studies with pig skin, ascorbic acid should be formulated at pH levels less than 3.5 to enter the skin. Tissue levels are saturated after three daily applications; the half-life of

tissue disappearance is about 4 days [28]. Derivatives of ascorbic acid including magnesium ascorbyl phosphate, ascorbyl-6-palmitate, and dehydroascorbic acid did not increase skin levels of ascorbic acid [28].

In humans, ascorbic acid taken orally is absorbed in the gastro-intestinal tract by an energy-requiring Na⁺-dependent active transport mechanism [11]. Active transport implies a saturable process and may decrease relative absorption if the intake is large. Thus, in humans, there is a limit of vitamin absorption. The average absorption was estimated at 80-90% of the dose. Thus, during the absorption process there is a loss in bioavailability of 10-20% [13].

Distribution, Metabolism and Elimination: After oral administration, ascorbic acid easily reaches the tissues. Plasma protein binding is around 25% [10]. Ascorbic acid accumulates in adrenal and pituitary glands [11]. The liver, spleen, brain and the optic lens contain appreciable concentrations of that vitamin. Ascorbic acid is excreted in the urine over a period of 10 days [11]. Ascorbic acid is reversibly oxidized to L-dehydroascorbic acid and partially metabolized to inactive sulphide and oxalic acid, which are expelled in urine [10]. Only in excess state is significant oxalate found in the urine, which accounts for one of the few potential clinical toxicities of systemic ascorbic acid supplementation, oxalic acid renal stones [13].

However, as vaginally applied vitamin C does not enter the systemic circulation in significant amounts, the distribution or elimination of Prevegyne[®] is not a major concern.

STORAGE AND STABILITY

Store at room temperature.

Store in a dry place.

Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each oval-shaped, white, controlled-release vaginal tablet contains 250 mg of ascorbic acid as an active ingredient and the following nonmedicinal ingredients: polydimethylsiloxane-methyltrisiloxane-copolymer, lactose monohydrate, hydroxypropylmethylcellulose, magnesium stearate and acetone.

This product does not contain ethanol, gluten, sulfite or tartrazine.

The tablets are packaged in blister strips. The blisters are inserted in folding cartons together with the package leaflets. A box contains six (6) tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

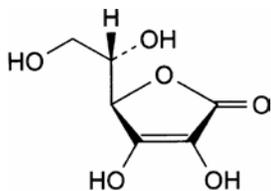
Drug Substance

Proper name: Ascorbic acid

Chemical name: (5R)-5-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one

Molecular formula and molecular mass: $C_6H_8O_6$
176.1

Structural formula:



Physicochemical properties: Ascorbic acid is freely soluble in water, soluble in alcohol, and practically insoluble in ether.

Ascorbic acid melts at about 190°C, with decomposition.

CLINICAL TRIALS

Study demographics and trial design

Three (3) double-blind, randomized, controlled studies, support the efficacy of ascorbic acid to reduce/relieve symptoms of non-specific vaginitis/bacterial vaginosis.

Table 4 - Summary of patient demographics for clinical trials in bacterial vaginosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)
A [Polatti <i>et al.</i> 2006]	Double blind, randomized, controlled	- 250 mg once/day - Vaginal - 6 days	39 ^a	30.6 ± 2.1
B [Petersen and Magnani 2004]	Double blind, randomized, placebo-controlled	- 250 mg once/day - Vaginal - 6 days	100 ^b	35.4 ± 10.4
C [Petersen 1998]	Double blind, randomized, placebo-controlled	- 250 mg once/day - Vaginal - 6 days	277 ^c	30.6 ± 2.1

^a Women with vaginal pH > 5, but without any clinical/microbiological evidence of vaginal infection, were enrolled.

^b All women enrolled were suffering from bacterial vaginosis with a vaginal pH ≥ 4.7.

^c 11 277 women were suffering from bacterial vaginosis.

Study results

Table 5 - Results of studies A, B and C in bacterial vaginosis (BV)

Study #	Primary Endpoints	Results
A [Polatti <i>et al.</i> 2006]	Vaginal pH-lowering effect of 3 different formulations each containing 250 mg vitamin C.	The study results confirm that vaginal application of vitamin C in 3 different formulations has an effective and long-lasting vaginal pH-lowering effect.
B [Petersen and Magnani 2004]	Presence of BV as assessed by at least 3 out of the 4 characteristic symptoms (vaginal discharge, malodour, vaginal pH ≥ 4.7 and presence of clue cells on microscopic examination of fresh smears) in placebo and vitamin C group, 1 and 2 weeks after the end of treatment.	After analysis of the 4 main symptoms, a statistically significant difference between the vitamin C and the placebo group was found; more patients were still affected by BV after placebo (35.7%) compared to patients treated with vitamin C tablets (14.0%).
C [Petersen 1998]	Percentage of patients suffering from none or up to 3 BV symptoms (reduction in intravaginal pH, absence of clue cells and negative amino test).	Vitamin C-treated patients in comparison to placebo showed a significant reduction in intravaginal pH, absence of clue cells and negative amino test. 55.5% of vitamin C-treated women were completely cured (no symptoms) vs. 25.7% of women who received placebo.

DETAILED PHARMACOLOGY

Prevegyne[®] vaginal tablets (each containing 250 mg of ascorbic acid) help to reduce/relieve symptoms of non-specific vaginitis/bacterial vaginosis. The special vaginal galenic formulation is capable of slowly releasing moderate amounts of ascorbic acid over hours in order to obtain a decrease of intravaginal pH and a consequent inhibition of all bacteria that cannot grow in a pH \leq 4 environment, in particular anaerobes that are undesirable. At the same time high local concentrations of ascorbic acid are lessened, thus reducing the risk of a significant irritation of the vaginal epithelium. Nonclinical studies related to the Prevegyne[®] indications are not present in the literature.

However, there is evidence in the literature, regarding the chemical and biological properties of ascorbic acid, which suggest that these vaginal tablets may be useful in the proposed indication: a) ascorbic acid can be applied vaginally to stimulate lactobacilli growth to the detriment of the uropathogens, which have a growth advantage over lactobacilli in the vaginal flora [29]; and b) ascorbic acid is capable of inhibiting the formation of nitrosamines, formed from amines and nitrites produced by the bacterial flora in the vaginal environment [21,22]. The generation of oncogenic nitrosamines in the human vagina, either independently or in association with human papilloma virus, has been associated with cervical intraepithelial neoplasia [30,31].

Moreover, a correlation between the release of ascorbic acid from the vaginal tablets and the pH of the dissolving medium was demonstrated in an *in vitro* study. Four clinical studies have shown the clinical efficacy and safety of Vagi-C (Prevegyne[®]) vaginal tablets [16,17,19,20] in 436 patients. Three of the studies were double-blind, randomized trials. The results showed that Vagi-C (Prevegyne[®]) is endowed with a prompt vaginal pH lowering effect, lasting for more than 12 hours from the product application. It also reduced other disturbances of nonspecific vaginitis, namely discharge and fishy odour. Treatment also induced a modification of the vaginal flora, with reduction of bacteria, disappearance of clue cells and increase of Lactobacilli [19,20]. In one study, 55% of the patients with aminocolpitis recovered following a six day treatment with once daily Vagi-C (Prevegyne[®]), while recovery was obtained in only 26% of patients receiving placebo [16].

Although formal safety pharmacology studies were not available, ascorbic acid even in amounts greatly in excess of the physiological requirements produces few if any pharmacodynamic effects. A possible risk of mega dosage treatments is represented by the formation of kidney stones [32].

MICROBIOLOGY

In the vagina, there is a dynamic microbiologic equilibrium. The *Lactobacillus acidophilus*, responsible for the acidic physiological pH of vaginal secretion, and the *Staphylococcus epidermis* dominate the flora, but many other species may be isolated from healthy individuals [33,34].

A disturbance in this dynamic microbiologic balance leading to characteristic changes in the vagina, but without inflammatory reaction is called bacterial vaginosis or nonspecific vaginitis

[33]. The main symptom in bacterial vaginosis is a foul-smelling vaginal discharge. Clinically objective criteria of bacterial vaginosis are: a homogeneous sticky greyish discharge with a typical fishy odour, a vaginal fluid with a pH \geq 4.5 and the presence of clue cells [35].

The mechanism of action of vaginally applied ascorbic acid is based on acidification of the vaginal fluid [16,17,19,20]. Decreased vaginal pH is detrimental for the survival of pathogenetic microorganisms, but not for *Lactobacillus acidophilus* that is responsible of the acidic vaginal pH and defends the host against pathogen colonization. Therefore, the vaginal application of ascorbic acid (250 mg) in the form of silicone-coated ascorbic acid tablets [19] ensures a long-lasting normalization of the vaginal flora. The special galenic formulation of this product guarantees efficient and controlled ascorbic acid release over hours, thereby reducing the risk of a significant irritation of the vaginal epithelium due to too high local ascorbic acid concentrations [16,17,19,20].

TOXICOLOGY

The literature dedicated to the toxicology of ascorbic acid is quite large, including more than 1,300 papers. The emphasis was mainly on mutagenicity, while there are few studies on the general toxicology, especially with long term exposure. The single dose toxicity after administration by any route to rodents, cats and dogs, was low. The lowest LD50 value was found in mice and guinea-pigs after intravenous administration: 500 mg/kg [36].

Scant information is available on general toxicity after repeated administration. A lot of mutagenicity studies were conducted on ascorbic acid [1]. On the whole, the weight of evidence indicates that ascorbic acid does not produce gene mutation in *Salmonella typhimurium* nor in mammalian cells using the mouse lymphoma assay [2,3]. Positive results were consistently obtained in *in vitro* assays for Sister-Chromatid Exchanges (SCE) and Unscheduled DNA Synthesis (UDS) induction, indicating the ability to produce DNA damage under certain conditions [4,5]. Negative results were obtained in *in vivo* assays, using high dose levels, for the induction of micronuclei and SCEs in bone marrow [6]. Two year carcinogenicity studies were performed in mice and rats in the context of the USA National Toxicology Program. The animals received diets containing 0, 25,000 and 50,000 ppm of ascorbic acid in three different groups. Under the conditions of this bioassay, ascorbic acid did not result carcinogenic in male and female rats and mice [7].

Due to the particular indications of Prevegyne[®], the reproductive and developmental toxicity studies of ascorbic acid are very important. A number of reproductive and developmental toxicity studies investigated the effects of ascorbic acid in the three different segments of reproduction in mice, rats and guinea pigs. The vitamin appeared devoid of adverse effects on reproduction parameters even at doses that are more than two orders of magnitude higher than those contained in Prevegyne[®] [14].

Ascorbic acid is devoid of irritating effects at the level of the skin and on the eye [15,12], but no studies were found investigating irritation at the level of the vaginal mucosa.

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PART III: CONSUMER INFORMATION

Prevegyne[®] Vaginal vitamin C tablets

This leaflet is part III of a three-part "Product Monograph" published when Prevegyne[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Prevegyne[®]. Contact your doctor, pharmacist or healthcare professional if you have any questions about this natural health product.

ABOUT THIS MEDICATION

What the medication is used for:

Prevegyne[®] helps to reduce/relieve symptoms of non-specific vaginitis/bacterial vaginosis.

What it does:

Prevegyne[®] is characterised by a special formulation that releases the vitamin over hours to allow an efficient action and at the same time to reduce the risk of an irritation of the vaginal epithelium by high ascorbic acid concentrations. It represents a modern approach for the decrease of the intravaginal pH value and for the consequent inhibition of all bacteria that cannot grow in a pH \leq 4 environment. Therefore, bacteria like lactobacilli (major constituents of the normal vaginal flora), capable of reproduction even at pH values below 4, are favoured.

When it should not be used:

You should not use Prevegyne[®] if:

- you are hypersensitive to ascorbic acid or to any ingredient in the formulation
- you are pregnant or breastfeeding

What the medicinal ingredient is:

The medicinal ingredient of Prevegyne[®] is vitamin C (ascorbic acid) 250 mg.

What the important nonmedicinal ingredients are:

Nonmedicinal ingredients are as follows: polydimethylsiloxane-methyltrisiloxane-copolymer, lactose monohydrate, hydroxypropylmethylcellulose, magnesium stearate and acetone.

What dosage forms it comes in:

Prevegyne[®] is supplied in the form of a controlled-release vaginal tablet. Each tablet contains 250 mg of ascorbic acid.

A box contains six (6) tablets.

WARNINGS AND PRECAUTIONS

If you have never been diagnosed with a bacterial vaginosis, it is recommended to consult your doctor, pharmacist or healthcare professional.

Vaginal use only. Do not swallow.

BEFORE you use Prevegyne[®] talk to your doctor, pharmacist or healthcare professional if you are:

- suffering from a vaginal infection due to Candida
- taking anticoagulants (blood thinners)
- suffering from hemolytic anemia (premature destruction of red blood cells)

Do not use if you are pregnant or breastfeeding.

INTERACTIONS WITH THIS MEDICATION

No interaction has been established with the intravaginal use of Prevegyne[®].

PROPER USE OF THIS MEDICATION

Usual dose:

Wash your hands thoroughly before and after inserting Prevegyne[®] vaginal tablets. Insert one (1) Prevegyne[®] tablet deeply into your vagina using your index and/or middle finger. To ease insertion it is recommended to insert the tablet in a lying position, preferably at bedtime. In order to decrease the risk of tablet breaking, a localized pressure should be applied at the edge of the blister (direct pressure in the center of the tablet should be avoided). The tip of a spoon or a fingernail may be used to gently break the foil underneath the blister.

The recommended dosage to help reduce/relieve symptoms of bacterial vaginosis is one (1) Prevegyne[®] vaginal tablet a day. A treatment of six (6) days is recommended to restore the physiological pH and the normal vaginal flora. If after six (6) days, you are still experiencing symptoms or if your symptoms increase while using Prevegyne[®], please consult your doctor or healthcare professional.

Prevegyne[®] tablets are a special vaginal formulation capable of slowly releasing moderate amounts of ascorbic acid over hours. Prevegyne[®] tablets should not be crushed or intentionally split.

In the event the tablet is accidentally split, both halves of the tablet should be used at once. For your comfort, insert both halves by their rounded parts.

Overdose:

Vitamin C inserted in the vagina is not absorbed in significant amounts. Only one (1) tablet should be inserted vaginally per day.

Missed Dose:

When a tablet has been missed, it should be inserted as soon as possible.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common adverse reactions associated with Prevegyn[®] are vaginal itching and burning. Other adverse reactions associated with Prevegyn[®] may include leucorrhoea (vaginal discharge), pain or insomnia.

This is not a complete list of side effects.

For any unexpected side effects while taking Prevegyn[®] contact your doctor, pharmacist or healthcare professional.

HOW TO STORE IT

Store at room temperature.

Store in a dry place.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect[™] Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. 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, Duchesnay Inc., at:

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Tel.: 1-888-666-0611
Fax: 1-888-588-8508
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