PRODUCT MONOGRAPH

Prevegyne®

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

Gynecological antiinfectives and antiseptics (G01AD03 Ascorbic Acid)

(NPN 80038565)
Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION ..........................................................3
  SUMMARY PRODUCT INFORMATION ........................................................................3
  INDICATIONS AND CLINICAL USE ........................................................................3
  CONTRAINDICATIONS ............................................................................................3
  WARNINGS AND PRECAUTIONS ............................................................................3
  ADVERSE REACTIONS ............................................................................................5
  DRUG INTERACTIONS ............................................................................................8
  DOSAGE AND ADMINISTRATION ............................................................................9
  OVERDOSAGE .........................................................................................................10
  ACTION AND CLINICAL PHARMACOLOGY .........................................................10
  STORAGE AND STABILITY ....................................................................................12
  SPECIAL HANDLING INSTRUCTIONS ................................................................12
  DOSAGE FORMS, COMPOSITION AND PACKAGING ............................................12

PART II: SCIENTIFIC INFORMATION ............................................................................13
  PHARMACEUTICAL INFORMATION ........................................................................13
  CLINICAL TRIALS ..................................................................................................14
  DETAILED PHARMACOLOGY .................................................................................15
  MICROBIOLOGY .....................................................................................................15
  TOXICOLOGY ..........................................................................................................16
  REFERENCES ...........................................................................................................17

PART III: PATIENT PRODUCT INFORMATION .............................................................19
Prevegyne®

Vitamin C (ascorbic acid)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

Prevegyne is contraindicated for patients who have demonstrated hypersensitivity 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. Overall, 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. 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. Negative results were obtained in in vivo assays, using high dose levels, for the induction of micronuclei and SCEs in bone marrow.

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

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

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 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%. Ascorbic acid accumulates in adrenal and pituitary glands. 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.

Ophthalmologic
Ascorbic acid was found to be non-irritating to the eye in animal studies.

Renal
Ascorbic acid is reversibly oxidized to L-dehydroascorbic acid and partially metabolized to inactive sulphide and oxalic acid, which are expelled in urine. 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.

Sexual Function/Reproduction
Due to the particular indications of Prevegyne, 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 Prevegyne.

Skin
Ascorbic acid was found to be non-irritating to the skin in animal studies.

Special Populations

Pregnant Women:
Prevegyne should not be used during pregnancy.
A clinical study on 54 pregnant women was conducted with Vagi-C (Prevegyne). No special adverse events were detected during pregnancy. No complications were reported in the pregnancy outcomes.

**Nursing Women:**
Prevegyne should not be used during nursing/breastfeeding.

Use in breastfeeding has not been studied.

Ascorbic acid is present in breast milk after oral administration. 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.

**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. 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. 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. Thirty out of 277 women (11.1%) were pregnant. One tablet was applied once a day for six (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 aborts. Twenty-four pregnant women considered of high risk to suffer from bacterial vaginosis and therefore preterm delivery and aborts were treated with Vagi-C (Prevegyne) once per day during several weeks. 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 (4) 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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 35 (%)</td>
<td>n= 50 (%)</td>
<td>n= 141 (%)</td>
<td>n= 24 (%)</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital Discharge</td>
<td>4</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>*</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning Sensation</td>
<td>5</td>
<td></td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidiasis</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

* 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
The following adverse events, listed alphabetically, have been reported during post-marketing experience with Prevegyne. Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship with the product.

Cardiac disorders: palpitations

Gastrointestinal disorders: abdominal distention, abdominal pain, constipation, dyspepsia, oropharyngeal blistering

General disorders and administration site conditions: asthenia, burning sensation, chills, condition aggravated, disease recurrence, fatigue, pain, pyrexia

Musculoskeletal and connective tissue disorders: muscle fatigue
Nervous system disorders: headache, paraesthesia

Psychiatric disorders: insomnia

Renal and urinary disorders: dysuria, micturition urgency, pollakiuria

Reproductive system and breast disorders: genital burning sensation, genital candidiasis, menstruation delayed, vaginal discharge, vaginal exfoliation, vaginal haemorrhage, vaginal infection, vaginal odour, vulval edema, vulvovaginal burning sensation, vulvovaginal discomfort, vulvovaginal dryness, vulvovaginal pain, vulvovaginal pruritus

Skin and subcutaneous tissue disorders: erythema, pruritus

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 2. Ascorbic acid solutions should not be mixed with salts of metals, especially copper and iron and oxidizers. 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 2.

Table 2 - Established or Potential Drug-Drug Interactions with Ascorbic Acid (Vitamin C) after Oral Administration

<table>
<thead>
<tr>
<th>Proper name</th>
<th>Effect</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and other anti-inflammatory drugs, or oral contraceptives</td>
<td>Reduce</td>
<td>Salicylates stimulate ascorbic excretion; more ascorbic acid is needed</td>
</tr>
<tr>
<td>Warfarin (Coumadin®) or heparin</td>
<td>Reduce</td>
<td>High-dose ascorbic acid might reduce their effectiveness</td>
</tr>
<tr>
<td>Iron supplements</td>
<td>Enhance</td>
<td>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</td>
</tr>
<tr>
<td>Medications in the nitrate family</td>
<td>Additive</td>
<td>Ascorbic acid may help to maintain their effectiveness</td>
</tr>
<tr>
<td>Protease inhibitors for HIV</td>
<td>Reduce</td>
<td>High-dose ascorbic acid may reduce their effectiveness</td>
</tr>
<tr>
<td>Cancer chemotherapy</td>
<td>Reduce</td>
<td>Do not use ascorbic acid except on physician’s advice</td>
</tr>
</tbody>
</table>
**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 six 6 days. However, following oral administration, ascorbic acid may alter the measurements of urine glucose, lactate dehydrogenase, serum transaminase and serum bilirubin.

**DOSAGE AND ADMINISTRATION**

**Dosing Considerations**
Prevegyne is for vaginal use only. It should not be taken by mouth.

**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**
Prevegyne tablets are a special vaginal galenic formulation capable of slowly releasing moderate amounts of ascorbic acid over hours. 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.

Prevegyne tablets should not intentionally be crushed or split. In the event the tablet is accidently split, both halves of the tablet should be used to ensure complete dosage administration. For a better comfort, both halves can be inserted by their round parts.

To ease insertion it is recommended to insert the tablet in a lying position, preferably at bedtime to avoid vaginal leakage, by using a vaginal applicator or the index and/or middle finger.

**With Applicator**
Prior to and after insertion of each Prevegyne vaginal tablet, patient should wash her hands and make sure the applicator has been cleaned using a fragrance free soap, rinsed and dried with a clean cloth. The inside piece of the applicator should be slightly pulled back to place the tablet into applicator. To avoid tablet from falling; ensure approximately 2/3 of the tablet fits within the applicator. One (1) Prevegyne tablet is to be inserted deeply in the vagina. Holding the
applicator in place, patient should gently push on the inside piece of the applicator to release the tablet into vagina.

**Without Applicator**
The patient is to wash her hands prior to and after insertion of the tablet into vagina. One (1) Prevegyne tablet is to be inserted deeply in the vagina using the index and/or middle finger.

**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 $^{14}$C-radiolabeled vitamin C to guinea pigs, the radioactivity peak in plasma was reached in 1.5h and terminal half-life was 61h. 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 CO$_2$, 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. 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 ensures a long-lasting normalization of the vaginal flora. The special galenic formulation of this product provides 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.

**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. This is based on the Tolerable Upper Intake Level which applies to total vitamin C (ascorbic acid) intake from
food and supplements.

**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. 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. Ascorbic acid and its metabolites were collected by microdialysis and assessed by gas chromatography mass spectrometry. 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. 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. No degradation of ascorbic acid was detected. Ascorbic acid remained stable and metabolites were not formed. 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. Derivatives of ascorbic acid including magnesium ascorbyl phosphate, ascorbyl-6-palmitate, and dehydroascorbic acid did not increase skin levels of ascorbic acid.

In humans, ascorbic acid taken orally is absorbed in the gastro-intestinal tract by an energy-requiring Na⁺-dependent active transport mechanism. 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%.

**Distribution, Metabolism and Elimination:** After oral administration, ascorbic acid easily reaches the tissues. Plasma protein binding is around 25%. Ascorbic acid accumulates in adrenal and pituitary glands. 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. Ascorbic acid is reversibly oxidized to L-dehydroascorbic acid and partially metabolized to inactive sulphide and oxalic acid, which are expelled in urine. 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.

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 and sight 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 isopropanol.

Prevegyne (ascorbic acid) 250 mg controlled-release tablets is available in blister strips. Two blister strips of three (3) tablets are inserted in a box. Each box contains six (6) tablets, one (1) plastic vaginal applicator and the patient product information leaflet.
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:  \( \text{C}_6\text{H}_8\text{O}_6 \)

176.1

Structural formula:

\[ \text{\includegraphics[width=0.5\textwidth]{structural_formula}} \]

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 3 - Summary of patient demographics for clinical trials in bacterial vaginosis

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

<sup>a</sup> Women with vaginal pH > 5, but without any clinical/microbiological evidence of vaginal infection, were enrolled.
<sup>b</sup> All women enrolled were suffering from bacterial vaginosis with a vaginal pH ≥ 4.7.
<sup>c</sup> All 277 women were suffering from bacterial vaginosis.

Study results

Table 4 - Results of studies A, B and C in bacterial vaginosis (BV)

<table>
<thead>
<tr>
<th>Study #</th>
<th>Primary Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>A [Polatti et al. 2006]</td>
<td>Vaginal pH-lowering effect of 3 different formulations each containing 250 mg vitamin C.</td>
<td>The study results confirm that vaginal application of vitamin C in 3 different formulations has an effective and long-lasting vaginal pH-lowering effect.</td>
</tr>
<tr>
<td>B [Petersen and Magnani 2004]</td>
<td>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.</td>
<td>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%).</td>
</tr>
<tr>
<td>C [Petersen 1998]</td>
<td>Percentage of patients suffering from none or up to 3 BV symptoms (reduction in intravaginal pH, absence of clue cells and negative amino test).</td>
<td>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.</td>
</tr>
</tbody>
</table>
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. The slow and controlled release of ascorbic acid also prevents high local concentration of ascorbic acid, 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.

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; 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. 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.

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 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. 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.

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.

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.

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. 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 ≥ 4.5 and the presence of clue cells.

**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 median lethal dose (LD50) value was found in mice and guinea-pigs after intravenous administration: 500 mg/kg.

Scant information is available on general toxicity after repeated administration. A lot of mutagenicity studies were conducted on ascorbic acid. Overall, 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. 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. Negative results were obtained in *in vivo* assays, using high dose levels, for the induction of micronuclei and SCEs in bone marrow. 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.

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.

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

   in vitro and in vivo Mutation Research 1983;117:83.
3. Amacher DE, Paillet S. Ascorbate is not detectably mutagenic in the L5178Y TK+/-
4. Galloway SM, Painter RB. Vitamin C is positive in the DNA synthesis inhibition and
5. Perry PE, Thomsen E. Evaluation of the SCE method in mammalian cells as a screening
   system for carcinogens in "Evaluation of Short-Term Test for Report of an International
6. Tsuchimoto T, Matter, B.E. Activity of coded compounds in the micronucleus test. In
   "Evaluation of Short-Term Test for Carcinogens: Report of an International Collaborative
7. Fielding Douglas J, Huff J, Peters AC. No evidence of carcinogenicity for L-ascorbic
8. Omaye ST. Safety of megavitamin therapy. In “Nutritional and toxicological aspects of
9. Naidu KA. Vitamin C in human health and disease is still a mystery? An overview Nutr J
10. Kleszczewska E. L-ascorbic acid - clinical use, toxicity, properties, methods of
11. Hornig D. Metabolism and requirements of ascorbic acid in man. S Afr Med J.
    Set on L-Ascorbic Acid (Vitamin C)”. Available from
13. Colven RM, Pinell SR. Topical Vitamin C in Aging. Clinics in Dermatology
    1996;14:226-34.
14. Frohberg VH, Gleich J, Kiesere H. Reproduction toxicology studies with Ascorbic Acid
    Set on L-Ascorbic Acid (Vitamin C)”. Available from
16. Petersen EE. Der Einsatz von Vitamin C (Vagi-C) zur Normalisierung der Vaginalflora.
17. Petersen EE. Prophylaxe durch intravaginale applikation von L-Askorbinsäure. Gyne
18. Byerley LO, Kirksey A. Effects of different levels of vitamin C intake on the vitamin C
    concentration in human milk and the vitamin C intakes of breast-fed infants. Am J Clin
19. Petersen EE, Magnani P. Efficacy and safety of vitamin C vaginal tablets in the treatment
    of non-specific vaginitis. A randomized, double blind, placebo controlled study. Eur J
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Prevegyne®
Vaginal vitamin C tablets
250 mg

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

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 tablets are a special vaginal formulation capable of slowly releasing moderate amounts of vitamin C over hours. Its special characteristic reduces the risk of irritation of the vaginal walls caused by high vitamin C concentrations.

Prevegyne helps restore vaginal flora by decreasing intravaginal pH (≤ 4). A pH below 4 favors good bacteria like lactobacilli (major constituents of the normal vaginal flora), capable of growing even at pH values ≤ 4. Decreased vaginal pH also limits the survival of pathogenic bacteria that negatively affect vaginal environment.

When it should not be used:
You should not use Prevegyne if:
- you are hypersensitive to ascorbic acid or to any ingredient in the product.
- you are pregnant or breastfeeding.

What the medicinal ingredient is:
Vitamin C (ascorbic acid).

What the nonmedicinal ingredients are:
Polydimethylsiloxane-methyltrisiloxane-copolymer, lactose monohydrate, hydroxypropylmethylcellulose, magnesium stearate and isopropanol.

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.

Prevegyne 250 mg tablets is available in blister strips. Two (2) blister strips of three (3) tablets are inserted in a box. Each box contains six (6) tablets, one (1) plastic applicator and the package leaflet.

WARNINGS AND PRECAUTIONS

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

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

Prevegyne is for vaginal use only. It should not be taken by mouth.

Prevegyne tablets should not intentionally be crushed or split.

To ease insertion it is recommended to insert the tablet in a lying position, preferably at bedtime to reduce vaginal leakage, by using a vaginal applicator or your index and/or middle finger.

With Applicator
Prior to and after insertion of each vaginal Prevegyne tablet, you should wash your hands and make sure both pieces of the applicator has been cleaned using a fragrance-free soap, rinsed and dried with a clean cloth (Figure 1).

To begin treatment:
- Delicately remove one (1) tablet from the blister strip. 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.
- Gently pull back the inside piece of the applicator until you feel a slight resistance. Place tablet vertically in the top of the applicator (Figure 2). To avoid tablet from falling, ensure approximately 2/3 of the tablet fits within the top of applicator.
- In a lying position, gently insert the applicator into your vagina as far as it will comfortably go. Holding the applicator in place, gently push the inside piece of the applicator (Figure 3). This will release the tablet in the vagina. Remove the applicator.
- Make sure to wash your hands and clean both pieces of the applicator with warm water and fragrance-free soap after each insertion. To clean, pull apart inside and outside pieces of applicator.

Once completely dry, gently push the inside piece into the outside piece of the applicator. Make sure to keep clean until next use.
The applicator is for personal use only. Therefore, in order to prevent infections, it should not be shared with others.

Dispose of the applicator after completion of the 6 day treatment.

**Without Applicator:**
Wash your hands thoroughly before inserting Prevegyne vaginal tablets.

To begin treatment:
- Delicately remove one tablet from the blister strip. 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. Prevegyne tablets should not intentionally be crushed or split.
- In a lying position, insert one (1) Prevegyne tablet into your vagina, as far as it will comfortably go using your index and/or middle finger.
- Wash your hands thoroughly after inserting Prevegyne vaginal tablets.

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.

In the event the tablet is accidently 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. Only one (1) tablet should be inserted vaginally per day. Dose should not be doubled nor two (2) tablets be inserted at once to catch-up the missed dose.

---

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

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

This is not a complete list of side effects.

For any unexpected side effects while taking Prevegyne contact your doctor, pharmacist or healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

**HOW TO STORE IT**

Store at room temperature. Store in a dry place.

Keep out of reach and sight of children.

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Duchesnay Inc. at:

950, boul. Michèle-Bohec  
Blainville, Québec, Canada  
J7C 5E2  
Tel: 1-888-666-0611  
Fax: 1-888-588-8508  
www.duchesnay.com

This leaflet was prepared by Duchesnay Inc.

Last revised: April 12, 2018.