NUVESSA 1.3% Vaginal Gel

Summary of Product Characteristics

1. Name of the medicinal product

Nuvessa

2. Qualitative and quantitative composition

Metronidazole 1.3% w/w, 65 mg of metronidazole in 5 grams of gel in a pre-filled applicator.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Vaginal gel.

Slightly opaque, yellow gel.

4. Clinical particulars

4.1 Therapeutic indications

Nuvessa is indicated for the treatment of bacterial vaginosis in females 12 years of age and older.

4.2 Posology and method of administration

A single-dose, pre-filled disposable applicator (which delivers approximately 5 g of gel containing 65 mg of metronidazole) administered once intravaginally. Nuvessa should be administered at bedtime.

Nuvessa is not for ophthalmic, dermal or oral use.

Instructions for use

Step 1: Remove the pre-filled applicator and plunger from the foil package.

Step 2: Insert the plunger into the open end of the pre-filled applicator.

- With the pink cap still on, push the tip of the plunger into the open end of the pre-filled applicator.

Step 3: Remove the pink cap.

- Pull the pink cap straight off the top of the pre-filled applicator.

Step 4: Prepare to insert the pre-filled applicator.

- The pre-filled applicator may be inserted while lying on your back with your knees bent or in any comfortable position.

Step 5: Insert the pre-filled applicator.

- Hold the pre-filled applicator by the barrel and gently insert the rounded tip into your vagina as far as it will comfortably go, then pull back slightly.

Step 6: Push the plunger.

- While holding the barrel in place, slowly press the plunger until it stops to release the gel into your vagina.

Step 7: Remove the pre-filled applicator from your vagina and throw it away in your household trash.

4.3 Contraindications

Hypersensitivity

Nuvessa is contraindicated in persons who have shown hypersensitivity to metronidazole, parabens, other ingredients of the formulation, or other nitroimidazole derivatives.

Use of disulfiram

Psychotic reactions have been reported with co-administration of disulfiram and oral metronidazole. Do not administer concurrently with or within 2 weeks of disulfiram.

Concomitant alcohol

Disulfiram-like reactions to alcohol have been reported with co-administration of oral metronidazole; do not consume ethanol or propylene glycol, during and for at least 24 hours following treatment.

4.4 Special warnings and precautions for use

Central and Peripheral Nervous System Effects

Convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral or intravenous metronidazole. Nuvessa should be administered with caution to patients with central nervous system diseases. Discontinue promptly if abnormal neurologic signs develop

Carcinogenicity in Animals

Metronidazole has been shown to be carcinogenic at high doses administered orally in mice and rats. Unnecessary use of metronidazole should be avoided. Use of Nuvessa should be reserved for the treatment of bacterial vaginosis.

Pediatric Use

The safety and effectiveness of Nuvessa have been established in pediatric subjects between the ages of 12 and less than 18 years old. Use of Nuvessa in this age group is supported by evidence from a multicenter, open-label safety and tolerability study in 60 pediatric subjects with bacterial vaginosis and, evidence from adequate and well-controlled studies in adult women,
The safety and effectiveness of Nuvessa in pediatric subjects below the age of 12 years have not been established.

Geriatric Use
Clinical studies with Nuvessa did not include sufficient numbers of subjects 65 years of age or older to determine whether they respond differently than younger subjects.

4.5 Interaction with other medicinal products and other forms of interaction

The intravaginal administration of a single dose of Nuvessa results in lower systemic exposure to metronidazole that is approximately 2% to 4% of that achieved following oral administration of 500 mg metronidazole tablets. The following drug interactions were reported for oral metronidazole.

Disulfiram
Use of oral metronidazole has been associated with psychotic reactions in alcoholic patients who are using disulfiram concurrently. Nuvessa should not be used by patients who have taken disulfiram within the last two weeks.

Alcoholic Beverages
Use of oral metronidazole has been associated with a disulfiram-like reaction (abdominal cramps, nausea, vomiting, headaches, and flushing) to alcohol. Alcoholic beverages and preparations containing ethanol or propylene glycol should not be consumed during and for at least 24 hours after Nuvessa therapy.

Coumarin and Other Oral Anticoagulants
Use of oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when Nuvessa is prescribed for patients on this type of anticoagulant therapy.

Lithium
Short-term use of oral metronidazole has been associated with elevation of plasma lithium concentrations and, in a few cases, signs of lithium toxicity in patients stabilized on relatively high doses of lithium.

Cimetidine
Use of oral metronidazole with cimetidine may prolong the half-life and decrease plasma clearance of metronidazole. No dose adjustment of Nuvessa is necessary.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary
There are no data available on the use of Nuvessa in pregnant women. Metronidazole usage in pregnancy has been associated with certain congenital anomalies (*see Data*). In animal reproduction studies, no fetotoxicity or teratogenicity was observed when metronidazole was administered orally, during organogenesis to pregnant rats and rabbits at up to 60 times and 30 times the recommended human dose based on body surface area comparison, respectfully (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data
Human Data
Blood levels following Nuvessa vaginal administration are lower than those achieved with oral metronidazole. Following a single intravaginal 5 g dose of Nuvessa, mean maximum concentration (C_{max}) and total exposure ($AUC_{0-\infty}$) are approximately 2% and 4%, respectively, of those following a single oral 500 mg dose of metronidazole tablets. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly.

There are published data from case-control studies, cohort studies, and 2 meta-analyses that include more than 5000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole in utero; however, these findings were not confirmed.

In addition, more than ten randomized placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy.

Three studies conducted to assess the risk of infant cancer following metronidazole exposure during pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited.

Animal Data
No fetotoxicity or teratogenicity was observed when metronidazole was administered orally to pregnant rabbits at up to 200 mg/kg (about 60 times the maximum human dose based on body surface area comparison). Similarly, no fetotoxic or teratogenic effects were observed in five studies in rats where dosing was administered orally in the diet or by gastric intubation at doses up to 200 mg/kg (about 30 times the maximum human dose based on body surface area comparison).

As well, no fetotoxicity or teratogenicity was observed when metronidazole was administered orally to pregnant mice at doses up to 100 mg/kg (about 7 times the maximum human dose based on body surface area comparison). However, some intrauterine deaths were observed in Swiss Webster mice administered metronidazole intraperitoneally at doses up to 15 mg/kg (about 1 time the maximum human dose based on body surface area comparison). The relationship of these intraperitoneal findings in mice to the vaginal use of Nuvessa is unknown.

Lactation

Risk Summary
There is no information on the presence of metronidazole in human milk, or the effects on the breast-fed child, or the effects on milk production following intravaginal administration of Nuvessa. Metronidazole is present in human milk following oral metronidazole administration, at concentrations similar to plasma concentrations (see Data). Since some metronidazole is systemically absorbed following vaginal administration of NUVESSA, excretion in human milk following topical use is possible.

Because of the potential risk for tumorigenicity shown in animal studies with metronidazole, breastfeeding is not recommended during treatment with Nuvessa and for 2 days (based on half-life) after NUVESSA therapy ends (see Clinical Considerations).

Clinical Considerations
A nursing mother may choose to pump and discard her milk during Nuvessa therapy and for 2 days after Nuvessa therapy ends, and feed her infant stored human milk or formula.

Data
In a study of nursing mothers receiving oral metronidazole 600 (n=11) or 1200 (n=4) mg daily, mean maternaplasma concentrations were 5.0 and 12.5 mcg/mL, respectively, within 2 hours following administration; the milk: maternal plasma ratio was approximately 1.

4.7 Effects on ability to drive and use machines

Systemic administration of metronidazole may affect a driving and using machines. In comparison with systemic use, topical metronidazole is absorbed in vagina in low concentrations.

Nuvessa may cause dizziness, ataxia, fatigue and weakness, therefore may affect driving or operating machinery.

4.8 Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience
Clinical Trial Experience in Adult Subjects
The safety of Nuvessa was evaluated in a randomized, double-blind, vehicle-controlled study in subjects with bacterial vaginosis. A total of 321 non-pregnant females with a mean age of 33.4 years (range 18 to 67 years) received Nuvessa. Subjects were primarily Black/African American (58.3%) or White (39.3%). Subjects administered a single dose of Nuvessa at bedtime on the first day of the study.

There were no deaths or serious adverse reactions in this trial. Adverse reactions were reported by 19.0% of subjects treated with Nuvessa versus 16.1% of subjects treated with Vehicle Gel.

Adverse reactions occurring in ≥1% of subjects receiving NUVESSA were: vulvovaginal candidiasis (5.6%), headache (2.2%), vulvovaginal pruritus (1.6%), nausea (1.6%), diarrhea (1.2%), and dysmenorrhea (1.2%). No subjects discontinued treatment due to adverse reactions.

Other Metronidazole Formulations
Other Vaginal Formulations
Other reactions that have been reported in association with the use of other formulations of metronidazole vaginal gel include: unusual taste and decreased appetite.

Topical (Dermal) Formulations
Other reactions that have been reported in association with the use of topical (dermal) formulations of metronidazole include skin irritation, transient skin erythema, and mild skin dryness and burning. None of these adverse reactions exceeded an incidence of 2% of patients.

Oral and Parenteral Formulations

The following adverse reactions and altered laboratory tests have been reported with the oral or parenteral use of metronidazole:

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Nervous System: The most serious adverse reactions reported in patients treated with oral metronidazole have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. In addition, patients have reported syncope, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness, and insomnia.

Gastrointestinal: Abdominal discomfort, nausea, vomiting, diarrhea, an unpleasant metallic taste, anorexia, epigastric distress, abdominal cramping, constipation, “furry” tongue, glossitis, stomatitis, pancreatitis, and modification of taste of alcoholic beverages.

Genitourinary: Overgrowth of Candida in the vagina, dyspareunia, decreased libido, proctitis.
Hematopoietic: Reversible neutropenia, reversible thrombocytopenia.

Hypersensitivity Reactions: Urticaria; erythematous rash; Stevens-Johnson Syndrome, toxic epidermal necrolysis, flushing; nasal congestion; dryness of the mouth, vagina, or vulva; fever; pruritus; fleeting joint pains.

Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure, darkened urine.

4.9 Overdose

There is no human experience with overdosage of metronidazole vaginal gel. Vaginally applied Nuvessa could be absorbed in sufficient amounts to produce systemic effects.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gynecological anti-infectives and antiseptics

ATC code: G01 AF01

Metronidazole is a nitroimidazole antimicrobial agent that acts primarily against anaerobic bacteria and selected protozoa. The 5-nitro group on the metronidazole molecule is reduced by metabolically active anaerobes to its active state by the bacterial nitro-reductase enzyme after it diffuses into the bacterial cell. This results in the production of cytotoxic compounds that disrupt the helical structure of bacterial DNA thereby inhibiting bacterial nucleic acid synthesis which leads to cell death.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis.

Metronidazole is active *in vitro* against most isolates of the following organisms that have been reported to be associated with bacterial vaginosis:
Bacteroides spp.
Gardnerella vaginalis
Mobiluncus spp.
Peptostreptococcus spp.

5.2 Pharmacokinetic properties

Following a single, intravaginal 5 g dose of Nuvessa (equivalent to 65 mg of metronidazole) to 20 healthy female subjects, a mean maximum serum metronidazole concentration (C_{max}) of 239 ng/mL was observed (range: 114 to 428 ng/mL). The average time to achieve this C_{max} was 7.3 hours (range: 4 to 18 hours). This C_{max} is approximately 2% of the mean maximum serum concentration reported in healthy subjects administered a single, oral 500 mg dose of metronidazole tablets (mean C_{max} = 12,785 ng/mL).

The extent of exposure [area under the curve (AUC)] of metronidazole, when administered as a single intravaginal 5 g dose of Nuvessa (equivalent to 65 mg of metronidazole), was 5,434 ng•hr/mL (range: 1382 to 12744 ng•hr/mL). This $AUC_{0-\infty}$ is approximately 4% of the reported AUC of metronidazole following a single oral 500 mg dose of metronidazole (approximately 125,000 ng•hr/mL).

5.3 Preclinical safety data

Carcinogenesis Mutagenesis, Impairment of Fertility
Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic oral administration in mice and rats. Pulmonary tumors were reported in several mouse studies in which mice were dosed orally at 75 mg/kg and above (about 6 or more times the maximum recommended human dose based on mg/m^2). Malignant lymphoma was reported at 66 mg/kg and above (about 5 or more times the maximum recommended human dose based on mg/m^2). These tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). All these effects were statistically significant.

There were statistically significant increases in the incidence of mammary tumors, among female rats administered metronidazole at 270 mg/kg and above (about 40 times the maximum human dose based on mg/m^2). Hepatic adenomas and carcinomas were observed in rats administered 300 mg/kg (about 45 times the maximum human dose based on mg/m^2).

Two lifetime oral tumorigenicity studies in hamsters have been performed and reported to be negative at doses up to 80 mg/kg (about 10 times the maximum human dose based on mg/m^2).

Carcinogenesis studies have not been conducted with Nuvessa.

Although metronidazole has shown in vitro mutagenic activity in bacterial reverse mutation tests, it was negative in *in vitro* mammalian mutation systems including CHO/HGPRT and CH V79 lung cell assays. Metronidazole was not clastogenic *in vitro* chromosome aberration tests in CHO cells up to 5000 µg/mL but was positive in human and monkey peripheral blood lymphocytes at 0.1 µg/mL.

In general, numerous micronucleus studies in rats and mice have failed to demonstrate a potential for genetic damage up to single oral doses 3000 mg/kg in mice (about 225 times the maximum human dose based on mg/m^2). However, a dose dependent increase in the frequency of micronuclei was observed in CFW mice after intraperitoneal injections of up to 160 mg/kg (about 12 times the maximum human dose based on mg/m^2). Fertility studies have been performed in mice orally dosed up to 500 mg/kg (about 37 times the maximum human dose based on mg/m^2) revealed no evidence of impaired fertility.

While no effects on fertility were observed in female rats dosed intraperitoneally at doses up to 1000 mg/kg (about 300 times the maximum human dose based on mg/m^2), studies in male rats resulted in effects on testes and sperm production at oral doses of 100 mg/kg and above (about 30 times the maximum human dose based on mg/m^2).

6. Pharmaceutical particulars

6.1 List of excipients

Polyethylene Glycol 400, Benzyl Alcohol, Propylene Glycol, Methylparaben, Propylparaben, Polycarbophil, purified water.

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Do not freeze. Do not refrigerate.

7. Marketing authorization holder

Imported by Exeltis (Thailand) Co.,Ltd., Bangkok, Thailand

Manufactured by Laboratorios Liconsa S.A., Guadalajara, Spain

8. Marketing authorization number(s)

On process

9. Date of first authorization

On process

10. Date of revision of the text

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