SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Zidoval 7.5 mg/g vaginal gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Metronidazole 0.75% w/w, 7.5 mg/g
Excipients with known effect:
Methyl parahydroxybenzoate (E218) 0.8 mg/g
Propyl parahydroxybenzoate (E216) 0,2 mg/g
Propylene glycol (E1520) 30.0 mg/g.
For the full list of excipients and allergens, see section 6.1.

3 PHARMACEUTICAL FORM
Vaginal gel
A colourless to straw coloured gel

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Zidoval 7.5 mg/g vaginal gel is indicated for the treatment of bacterial vaginosis (formally called nonspecific vaginitis gardnella vaginalis vaginitis or haemophilus vaginitis).

4.2 Posology and method of administration
Posology
For vaginal administration.

Adults
One application of Zidoval 7.5 mg/g vaginal gel inserted into the vagina once daily, at bedtime, for 5 consecutive days.

Elderly
Bacterial vaginosis is not commonly seen in the elderly population and consequently clinical assessment in this age group has not been carried out.

Pediatric population
Not recommended for use in children and adolescents under 18 years since safety and efficacy have not been established.

Method of administration
Pierce sealed end of tube and screw open end of applicator tightly onto tube of gel. Squeeze tube, filling the applicator with gel. Remove applicator from tube and gently insert applicator into vagina as far as it will comfortably go. Push the plunger to release the gel. Dispose of applicator as instructed.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to other nitroimidazoles or parabens.

4.4 Special warnings and precautions for use

Use during menses is not recommended.
Known or previously unrecognised candidiasis may present more prominent symptoms during therapy with Zidoval 7.5 mg/g vaginal gel and may require treatment with acandicidal agent.
If irritation does occur the patient should be advised to use metronidazole less frequently or to stop temporarily and to seek medical advice if necessary.
Metronidazole is a nitroimidazole and should be used with care in patients with evidence of a history of blood dyscrasias.
As with all vaginal infections, sexual intercourse during the infection and during treatment with Zidoval 7.5 mg/g vaginal gel is not recommended.
Unnecessary and prolonged use of this medication should be avoided. Evidence suggests that metronidazole is carcinogenic in certain animal species. There is no evidence to date of a carcinogenic effect in human (see section 5.3 preclinical safety data).

Zidoval 7.5 mg/g vaginal gel contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).
Zidoval 7.5 mg/g vaginal gel also contains propylene glycol which may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Oral metronidazole has been associated with a disulfiram-like reaction in combination with alcohol. Acute psychotic reactions and confusion have occurred during concomitant use of disulfiram with oral metronidazole. At the low serum concentrations which result from the use of Zidoval 7.5 mg/g vaginal gel , the possibility of similar reactions is unlikely although cannot be excluded.Oral metronidazole has been shown to increase the plasma concentrations of warfarin and other coumarin anticoagulants resulting in a prolongation of prothrombin time.
The effect of topical metronidazole on prothrombin time is unknown. It has also been shown to increase the plasma concentrations of lithium, cyclosporin and 5- fluorouracil. Similar effects after vaginal administration of metronidazole are not expected due to the low plasma concentrations but cannot be completely ruled out.
Metronidazole may interfere with certain types of determination of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactic dehydrogenase (LDH), triglycerides and hexokinase glucose. Values of zero may be observed.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Data on a large number (several hundred) of exposed pregnancies indicate no adverse effects of metronidazole on the foetus/newborn child. There have been no formal studies with Zidoval 7.5 mg/g vaginal gel in pregnant women. Caution should, therefore, be exercised when prescribing to pregnant women.Breastfeeding
The ratio of serum concentrations of Zidoval 7.5 mg/g vaginal gel /oral metronidazole is approximately 0.02. Metronidazole is excreted in milk at concentrations similar to those in maternal serum and the ratio of serum concentrations of metronidazole in the breastfed infant/mother is approximately 0.15. Caution should be exercised when prescribing to lactating women.

4.7 Effects on ability to drive and use machines

Zidoval 7.5 mg/g vaginal gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

In controlled clinical trials involving 759 patients, the most commonly reported

ADRs were urogenital (26%) and gastrointestinal (14%).
The following adverse experiences have been reported, and within each system organ class, are ranked by frequency, using the following convention:
Very common (≥1/10)
Common (≥1/100, < 1/10)
Uncommon (≥ 1/ 1,000, < 1/100)
Rare (≥1/10,000, < 1/1,000)
Very rare (<1/10,000), including isolated reports

Infections and infestations
Common: Vaginal candidiasis.

Metabolism and nutrition disorders
Common: Decreased appetite.

Psychiatric Disorders
Uncommon: Depression, difficulty sleeping.

Nervous system disorders
Common: Headache, dizziness.
Uncommon: Paraesthesia, hypoesthesia, dysgeusia
(metallic taste).

Gastrointestinal disorders
Common: GI discomfort/abdominal cramps, vomiting, unpleasant taste/unusual feeling on tongue.
Uncommon: Diarrhoea, constipation, abdominal bloating/noises, nausea, dry mouth.

Skin and subcutaneous tissue disorders
Common: Dry skin, erythema, pruritus, skin discomfort (burning, pain of skin/stinging), skin irritation.
Not known Urticaria.

Musculoskeletal and connective tissue disorders
Uncommon: Cramp.

Renal and urinary disorders
Uncommon: Urine discolouration, urinary tract infection symptoms.

Reproductive system and breast disorders
Common: Vaginal itching/irritation/burning/numbness, pelvic discomfort, vaginal discharge.
Uncommon: Oedema vulva, menstrual discomfort/irregularities, vaginal spotting/bleeding.

General disorders and administration site conditions
Uncommon: Fatigue, irritability.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose
There is no human experience of overdosage with Zidoval 7.5 mg/g vaginal gel GEL . There is no specific treatment. Metronidazole is readily removed from the plasma byhaemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Gynecological anti-infectives and antiseptics
ATC code: G01 AF01
Metronidazole is a synthetic antibacterial agent which also possesses amoebicidal activity. Zidoval 7.5 mg/g vaginal gel has been shown in vivo to be active against the vaginal pathogens Gardnerella vaginalis and bacteroides species.Significant increases in lactobacilli are observed in bacterial vaginosis patients following therapy with Zidoval 7.5 mg/g vaginal gel .

5.2 Pharmacokinetic properties
Bioavailability studies on the administration of a single 5 gram dose of Zidoval 7.5 mg/g vaginal gel into the vagina of 12 normal subjects showed a mean C_{max} serum concentration of 237 nanogram/ml or about 2% of the mean maximum serum concentration of a 500 mg tablet taken orally (mean C_{max} = 12,785 ng/ml). Under normal usage, the formulation therefore affords minimal serum concentrations of metronidazole.
Metronidazole has a large apparent volume of distribution and has the ability to penetrate the blood brain barrier and blood cerebro-spinal fluid barrier at concentrations similar to serum concentrations.
Metronidazole is metabolised in the liver by side chain oxidation and glucuronide formation and a large portion of the absorbed dose is excreted as metabolites. Both unchanged drug and metabolites are excreted mainly in the urine.

5.3 Preclinical safety data
At high doses metronidazole has been found to be mutagenic in bacteria but not in mammalian cells *in vitro* or *in vivo*. A carcinogenic potential has been demonstrated in mouse and rat but not in hamster. In epidemiological studies, no evidence of increased risk of cancer as a consequence of exposure to metronidazole has been observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
propylene glycol, carbomer (Carbopol) 974P, parahydroxybenzoate methyl, sodium edetate, parahydroxybenzoate propyl, sodium hydroxide, purified water.

6.2 Incompatibilities
None known.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage
Do not store above 25 ºC.

6.5 Nature and contents of container
Aluminium tubes lined with an epoxy phenolic resin with polyethylene screw caps containing 40 g product. The product is packaged with 5 disposable vaginal applicators, each to deliver 5 g of gel.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Manufacturer
Meda Manufacturing SAS,
Avenue J F Kennedy, Merignac, France

8 MARKETING AUTHORISATION HOLDER
Megapharm Ltd.
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8 MARKETING AUTHORISATION NUMBER(S)
118-72-29887

9. Revised on 092020