

1. NAME OF THE MEDICINAL PRODUCT

Fortacin 150 mg/ml + 50 mg/ml cutaneous spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 150 mg lidocaine and 50 mg prilocaine.

Each container delivers a minimum of 20 doses (6.5 ml) or 12 doses (5.0 ml).

Each actuation delivers 50 microlitres which contains 7.5 mg lidocaine and 2.5 mg prilocaine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous spray, solution

Colourless to light yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fortacin is indicated for the treatment of primary premature ejaculation in adult men.

4.2 Posology and method of administration

Posology

The recommended dose is 3 actuations applied to cover the glans penis. Each dose consists of a total of 22.5 mg lidocaine and 7.5 mg prilocaine per application (1 dose is equal to 3 actuations).

A maximum of 3 doses can be used within 24 hours with at least 4 hours between doses.

Special populations

Elderly

Dosage adjustments are not required in the elderly.

There is limited data on the efficacy and safety of Fortacin in patients 65 years and over.

Renal impairment

Clinical studies have not been performed in patients with impaired renal function, however due to its method of administration and very low systemic absorption, no dosage adjustment is required.

Hepatic impairment

Clinical studies have not been performed in patients with impaired hepatic function, however due to its method of administration and very low systemic absorption, no dosage adjustment is required.

Caution is advised in case of severe hepatic impairment (see section 4.4).

Paediatric population

There is no relevant use of Fortacin in the paediatric population in the indication: treatment of primary premature ejaculation in adult men.

Method of administration

Cutaneous use.

Fortacin is only indicated for application to the glans penis.

Before initial use, the spray container should be briefly shaken and then primed it by spraying it into the air three times.

Before each subsequent use, it should be briefly shaken and then the spray container should be re-primed by spraying it once.

Any foreskin should be retracted from the glans penis. Once the can is held upright (valve up), 1 dose of Fortacin should be applied to the entire glans penis, by actuating the valve 3 times. One third of the glans penis should be covered with each actuation. After 5 minutes any excess spray should be wiped off prior to intercourse.

4.3 Contraindications

Hypersensitivity of the patient or their partner to the active substances or to any of the excipients listed in section 6.1.

Patients or their partner with a known history of sensitivity to local anaesthetics of the amide type.

4.4 Special warnings and precautions for use

Anaemia related conditions

Patients or their partner with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methaemoglobinaemia are more susceptible to medicinal product-induced methaemoglobinaemia (see section 4.5).

Although the systemic availability of prilocaine by cutaneous absorption of Fortacin is low, caution should be exercised in patients with anaemia, congenital or acquired methaemoglobinaemia or patients on concomitant therapy known to produce such conditions.

Interactions

Patients on anti-arrhythmic medicinal products class III (e.g. amiodarone) should be treated with caution.

Hypersensitivities

Patients allergic to paraaminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine; however, Fortacin should be used with caution in patients with a history (or partner with a history) of sensitivities to medicinal products, especially if the aetiologic agent is uncertain.

Precautions for use

Care should be taken not to allow Fortacin to come in contact with the eye, as it may cause eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of Fortacin in conjunctival tissues has not been determined. If contact with the eye occurs, immediately rinse the eye with water or sodium chloride solution and protect it until sensation returns.

Fortacin sprayed onto mucous membranes of the patient or their partner, such as the mouth, nose and throat, or transferred onto female genitalia or anal lining, could be absorbed and temporary local

numbness/anaesthesia is likely to result. This hypoaesthesia may mask normal pain sensations and, therefore, increase the dangers of localised injury.

Fortacin sprayed onto a damaged tympanic membrane may cause ototoxicity of the middle ear.

Deterioration was observed when Fortacin was used with polyurethane-based female and male condoms.

A higher rate of erectile dysfunction and male genital hypoaesthesia may be experienced when using Fortacin with male condoms.

Due to the risk of partner transfer, patients hoping to achieve conception should either avoid using Fortacin, or, if it is essential to achieve penetration, should wash the glans penis as thoroughly as possible 5 minutes after applying the spray but prior to intercourse (see section 4.6).

Patients with severe hepatic impairment

Patients with severe hepatic disease, because of their inability to metabolise local anaesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Methaemoglobinaemia may be accentuated in patients already taking medicinal products known to induce the condition, e.g. sulphonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapson, metoclopramide, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenobarbital, phenytoin, primaquine and quinine (see section 4.4).

The risk of additional systemic toxicity should be considered when large doses of Fortacin are applied to patients already using other local anaesthetics or structurally related medicinal products e.g. class I anti-arrhythmics such as mexiletine.

Specific interaction studies with lidocaine/prilocaine and anti-arrhythmic medicinal products class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).

Medicinal products that reduce the clearance of lidocaine (e.g. cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given intravenously in repeated high doses over a long time period (30 hours).

In vitro interaction studies with topical antifungal (clotrimazole, econazole, imidazole, nystatin, miconazole, ketoconazole), antibacterial (clindamycin, metronidazole) and antiviral medicinal products (acyclovir), showed no effect on antimicrobial activity.

4.6 Fertility, pregnancy and lactation

Fortacin is not indicated for use by women. However, there may be some exposure in female partners of men treated with Fortacin.

Women of childbearing potential / contraception in male and females

Patients hoping to achieve conception should either avoid using Fortacin, or, if it is essential to achieve penetration, should wash the glans penis as thoroughly as possible prior to intercourse.

Pregnancy

There are no or limited amount of data from the use of lidocaine and prilocaine in pregnant women. Animal studies do not indicate reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Fortacin during pregnancy unless effective male barrier contraceptive measures are taken in order to avoid potential foetal exposure.

Breast-feeding

Lidocaine and prilocaine are excreted in human milk, but at therapeutic doses of Fortacin no effects on the breastfed newborns/infants are anticipated due to active substance transfer from the male patient to his female partner.

Fertility

There are no adequate data from the use of lidocaine and prilocaine on fertility in humans. A study in rats showed that Fortacin caused a reduction in sperm motility. This medicinal product may reduce the possibility of pregnancy, but should not be used as a contraceptive.

4.7 Effects on ability to drive and use machines

Fortacin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Fortacin was evaluated based on 596 male patients who applied it during clinical trials. Safety has also been evaluated in 584 female partners of these subjects.

Adverse reactions occurred in 9.6% of male subjects and 6.0% of female partners. Most cases were classed as mild or moderate.

The most frequent adverse reactions reported with the use of this medicinal product in male patients were local effects of genital hypoaesthesia (4.5%) and erectile dysfunction (4.4%). These adverse reactions caused discontinuation of treatment in 0.2% and 0.5% of patients, respectively.

The most frequent adverse reactions reported with the use of this medicinal product in female partners were vulvovaginal burning sensation (3.9%), and genital hypoaesthesia (1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects.

Tabulated list of adverse reactions

Frequency of the adverse reactions is defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidence.

Adverse Drug Reactions in Male Glans-penis-treated Subjects		
System Organ Class	Frequency	Adverse Reactions
Psychiatric disorders	Uncommon	Abnormal orgasm
Nervous system disorders	Uncommon	Headache
Respiratory, thoracic and mediastinal disorders	Uncommon	Throat irritation
Skin and subcutaneous tissue disorders	Uncommon	Skin irritation
Reproductive system and breast disorders	Common	Hypoaesthesia of male genital,erectile dysfunction, genital burning sensation
	Uncommon	Genital erythema, ejaculation failure, paraesthesia of male genital, penile pain, penis disorder, pruritus genital
General disorders and administration site conditions	Uncommon	Pyrexia

Adverse Drug Reactions in Female Partners		
System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Uncommon	Vaginal candidiasis
Nervous system disorders	Uncommon	Headache
Respiratory, thoracic and mediastinal disorders	Uncommon	Throat irritation
Gastrointestinal disorders	Uncommon	Anorectal discomfort, oral parasthesia
Renal and urinary disorders	Uncommon	Dysuria
Reproductive system and breast disorders	Common	Vulvovaginal burning sensation, hypoaesthesia
	Uncommon	Vulvovaginal discomfort, vaginal pain, vulvovaginal pruritus

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

As Fortacin is applied topically to the glans penis the risk of overdose is low.

Prilocaine in high doses may cause an increase in the methaemoglobin level particularly in conjunction with methaemoglobin-inducing agents (e.g. sulphonamides). Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylthionium chloride.

Should other symptoms of systemic toxicity occur, the signs are anticipated to be similar in nature to those following the administration of local anaesthetics by other routes. Local anaesthetic toxicity is manifested by symptoms of nervous system excitation and, in severe cases, central nervous and cardiovascular depression.

Severe neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and the administration of anticonvulsive medicinal products.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, amides, ATC code: NO1BB20

Mechanism of action

Fortacin provides topical anaesthesia to the glans penis. The active substances lidocaine and prilocaine block the transmission of nerve impulses in the glans penis, reducing the sensitivity of the glans penis. This is translated into a delaying of the ejaculatory latency time without adversely affecting the sensation of ejaculation.

Pharmacodynamic effects

Clinical trials have shown Fortacin to increase the intra-vaginal ejaculatory latency time (IELT), increase control over ejaculation and reduce the feelings of distress in patients with premature ejaculation as measured by the Index of Premature Ejaculation (IPE). The medicinal product has a rapid onset of action and is effective within 5 minutes of application. The effectiveness of the medicinal product has been demonstrated to persist on repeat use over time.

Clinical efficacy and safety

The efficacy of Fortacin was demonstrated in two multi-centre, multinational, randomised, double-blind, placebo controlled studies, both followed by an open-label phase. Men satisfying the International Society for Sexual Medicine (ISSM) criteria for premature ejaculation (PE) who had a baseline IELT \leq 1 minutes in at least 2 of the first 3 sexual encounters during screening were eligible to enrol.

The effectiveness of Fortacin in treating PE was assessed by measuring IELT and the co primary endpoints of ejaculatory control, sexual satisfaction, and distress using the IPE. During the 3 months of the double-blind treatment phase, the geometric mean IELT increased from 0.58 to 3.17 minutes in the Fortacin group and from 0.56 to 0.94 minutes in the placebo group.

85.2% of subjects in the Fortacin group achieved a mean IELT of $>$ 1 minute over the course of 3 months of treatment with it, whereas 46.4% of the placebo subjects had a mean IELT of $>$ 1 minute. 66.2% of Fortacin-treated subjects and 18.8% of placebo-treated subjects achieved a mean IELT $>$ 2 minutes.

The clinically significant increases in IELT were paralleled by significant differences in the IPE scores ($p < 0.0001$). Adjusted mean change scores (Fortacin vs. placebo) at Month 3 were 8.2 vs. 2.2 for the ejaculatory control score, 7.2 vs. 1.9 for the sexual satisfaction score, and 3.7 vs. 1.1 for the distress score.

In Fortacin-treated subjects, IELT and IPE scores increased at the first measured timepoint. Both IELT and IPE scores continued to increase slightly more throughout the remainder of the double-blind

phase. The positive changes in IELT and IPE domain scores were maintained during the open-label treatment phase.

At each of the three monthly assessments all subjects completed a Premature Ejaculation Profile (PEP) questionnaire relating to perceived control over ejaculation, personal distress related to ejaculation, satisfaction with sexual intercourse, and interpersonal difficulty relating to ejaculation. The PEP scores followed a similar pattern of improvement to the IELT and IPE scores. For all of the three monthly assessments completed by the subjects, there was a significant difference between Fortacin and placebo ($p < 0.0001$). Partners completed the PEP questionnaire at month three. There was also a significant difference over placebo in all domains for the responses from the partners ($p < 0.0001$).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Fortacin in all subsets of the paediatric population in premature ejaculation (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The plasma levels of lidocaine and prilocaine in male and female subjects were below the level associated with toxicity (5000 ng/ml). Male volunteers had maximum plasma concentrations of lidocaine which were less than 4% of toxic levels, and prilocaine which were less than 0.4% of toxic levels, after repeat dosing. Female volunteers receiving repeated doses directly to the cervix and vagina of up to five times the recommended dose for the male partner, had maximum plasma levels of lidocaine which were less than 8% of toxic levels, and prilocaine which were less than 1% of toxic levels.

Systemic exposure to lidocaine and prilocaine and their metabolites (respectively 2,6-xylidine and *o*-toluidine), is low following application to the glans penis in male patients and application to the cervix/vagina fornices in female subjects, at doses higher than recommended.

Distribution

Lidocaine

The steady-state volume of distribution is 1.1 to 2.1 L/kg after intravenous administration. Lidocaine is reported to be 66% bound by plasma proteins, including alpha-1-acid glycoprotein. Lidocaine can cross the blood brain barrier and the placenta and is distributed in breast milk.

Prilocaine

Following intravenous administration, the steady state volume of distribution of prilocaine is 0.7 to 4.4 L/kg. Prilocaine is reported to be 55% bound to plasma proteins, including alpha-1-acid glycoprotein. Prilocaine crosses the blood-brain barrier and also crosses the placenta. Prilocaine is also distributed in breast milk.

Biotransformation

Lidocaine is largely metabolised in the liver by cytochrome P450 (CYP 3A4) and probably to a minor extent in the skin. First pass metabolism is rapid and extensive and bioavailability is about 35% after oral doses.

Prilocaine is rapidly metabolised in both the liver, by cytochrome P450, and in the kidneys by amidases.

The metabolism of lidocaine and prilocaine results in the formation of 2,6-xylylidine and *o*-toluidine, respectively, amongst other metabolites. Plasma levels of these metabolites detected after administration of Fortacin in clinical trials were low in both male and female subjects, even after doses of it many times in excess of the clinical dose were applied. No 2,6-xylylidine or *o*-toluidine was detectable at any time-point in vaginal fluids following local application of the medicinal product in female volunteers.

Elimination

Lidocaine

The terminal elimination half-life of lidocaine from the plasma following intravenous administration is approximately 65 - 150 minutes and the systemic clearance is 10 - 20 mL/min/kg. Lidocaine is excreted in the urine mainly as metabolites, with only a small proportion excreted unchanged.

Prilocaine

The elimination half-life of prilocaine following intravenous administration is approximately 10 - 150 minutes. The systemic clearance is 18 - 64 mL/min/kg. Prilocaine is excreted in the urine mainly as its metabolites, with only a small proportion excreted unchanged.

5.3 Preclinical safety data

Reproductive toxicity

Lidocaine

No teratogenic effects were observed in studies of embryonic/foetal development in rats and rabbits receiving doses during organogenesis. Embryotoxicity was observed in rabbits at doses toxic to the mother. The postnatal survival time of the offspring of rats treated during pregnancy and lactation with a dose toxic to the mother was shown to be reduced.

Prilocaine

In a study of pregnant rats receiving a combination of lidocaine and prilocaine during organogenesis, no effects on embryonic/foetal development were observed. There are however no systemic exposure data available for comparison with clinical exposure.

Genotoxicity and carcinogenicity

Lidocaine

Lidocaine was not genotoxic and the carcinogenic potential of lidocaine has not been studied. The lidocaine metabolite 2,6-xylylidine has genotoxic potential *in vitro*. In a carcinogenicity study of rats exposed to 2,6-xylylidine *in utero*, postnatally and throughout their lifetime, tumours in the nasal cavity, subcutaneous tumours and liver tumours were observed. The clinical relevance of tumour findings in relation to short-term/intermittent use of lidocaine in humans is unknown. Human exposure from Fortacin is 20-30 fold less than the minimum dose that did not result in tumours and 200 fold less than the minimum dose that did result in tumours.

Prilocaine

Prilocaine was not genotoxic and the carcinogenic potential of prilocaine has not been studied. The

prilocaine metabolite *o*-toluidine has genotoxic potential *in vitro*. In carcinogenicity studies of *o*-toluidine in rats, mice and hamsters, tumours were observed in several organs. The clinical relevance of tumour findings in respect of short-term/intermittent use of prilocaine in humans is unknown. Human exposure is 1000 fold less than than the minimum dose studied. Note, this dose did result in tumours.

Effect on fertility

In an *in vitro* study of rats Fortacin has shown a reduction in sperm motility when 22.5 mg lidocaine and 7.5 mg prilocaine (i.e. the amount in 1 human dose) was in direct contact with rat sperm. However this study did not reproduce the circumstances of clinical use, as the concentration of Fortacin in direct contact with the sperm would be many fold lower. The potential for reduction of sperm motility following the clinical use of the medicinal product can not be excluded; therefore it is not possible to state whether Fortacin would prevent pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane

6.2 Incompatibilities

Deterioration was observed when Fortacin was used with polyurethane-based female and male condoms (see section 4.4).

6.3 Shelf life

18 months.

After first use: 12 weeks

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Each pack contains one aluminium spray container with metering valve containing 6.5 ml or 5.0 ml solution.

6.6 Special precautions for disposal and other handling

The metal container is pressurised. It should not be punctured, broken or burnt, even when apparently empty.

A residual volume of fluid that is not usable will remain in the container after all doses have been administered.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/881/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 November 2013

10. DATE OF REVISION OF THE TEXT

05/2016

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>