EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/418487/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fortacin

International non-proprietary name: lidocaine / prilocaine

Procedure No. EMEA/H/C/002693/II/0030

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	14 Oct 2019	14 Oct 2019	☐
☐	CHMP Rapporteur Assessment Report	12 Nov 2019	13 Nov 2019	☐
☐	PRAC Rapporteur Assessment Report	15 Nov 2019	13 Nov 2019	☐
☐	PRAC members comments	20 Nov 2019	20 Nov 2019	☐
☐	Updated PRAC Rapporteur Assessment Report	21 Nov 2019	21 Nov 2019	☐
☐	PRAC endorsed relevant sections of the assessment report	28 Nov 2019	28 Nov 2019	☐
☐	CHMP members comments	02 Dec 2019		☐
☐	Updated CHMP Rapporteur Assessment Report	05 Dec 2019	05 Dec 2019	☐
☐	Request for supplementary information (RSI)	12 Dec 2019	12 Dec 2019	☐
☐	CHMP Rapporteur Assessment Report	25 Feb 2020	26 Feb 2020	☐
☐	PRAC Rapporteur Assessment Report	28 Feb 2020	26 Feb 2020	☐
☐	PRAC members comments	04 Mar 2020	04 Mar 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	05 Mar 2020	N/A	☐
☐	PRAC endorsed relevant sections of the assessment report	12 Mar 2020	12 Mar 2020	☐
☐	CHMP members comments	16 Mar 2020	16 Mar 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	19 Mar 2020	20 Mar 2020	☐
☐	2nd RSI	26 Mar 2020	26 Mar 2020	☐
☐	Deadline for submission	23 Jun 2020	23 Jun 2020	☐
☐	Re-start of procedure	24 Jun 2020	24 Jun 2020	☐
☐	PRAC Rapporteur Assessment Report	29 Jun 2020	n/a	☐
☐	Comments from PRAC	01 Jul 2020	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	02 Jul 2020	n/a	☐
☐	CHMP Rapporteur Assessment Report	08 Jul 2020	08 Jul 2020	☐
☐	PRAC outcome	09 Jul 2020	n/a	☐
☐	Comments from CHMP	13 Jul 2020	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Jul 2020	n/a	☐
☒	Opinion	23 Jul 2020	23 Jul 2020	☐

Procedure resources	
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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Recordati Ireland Ltd submitted to the European Medicines Agency on 25 September 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.5.b	C.I.5.b - Change in the legal status of a medicinal product for centrally authorised products - All other legal status changes	Type II	I, II, IIIA and IIIB

Change in the legal status of Fortacin from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription'. Furthermore, the PI is being brought in line with the latest QRD template (version 10.1). The RMP version 3.1 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

Fortacin containing the active substances lidocaine (150 mg/ml) and prilocaine (50 mg/ml) is a cutaneous spray solution indicated in the treatment of primary premature ejaculation (PE) in adult men. It 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.

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.

Fortacin was approved in the European Union (EU) on 15 November 2013 and it was first marketed in the UK in November 2016 followed by Italy, France, Spain, Germany and Portugal in 2018. Cumulatively, 58,431 patients have been exposed to the product. This number is based on an estimation from the number of cutaneous spray and pack units sold and therefore may reflect an overestimation.

PE is a prevalent male sexual disorder and causes a high level of bother and distress. It has been classified into two forms: a primary (lifelong) form that begins when a male first becomes sexually active and a secondary (acquired) form[1]. Pharmacotherapy is the basis of treatment in life-long PE. In acquired PE, it is recommended to treat also the associated condition, such as erectile dysfunction (ED) or prostatitis.

Dapoxetin, a selective serotonin reuptake inhibitor (SSRI), and a number of topical anaesthetics containing lidocaine or lidocaine/prilocaine are currently authorised for the treatment of PE. The MAH has provided information about several medicinal products containing mainly lidocaine that have been available as non-prescription medicines for many years, some as sprays and others as creams.

In the current application the MAH proposes to change the legal status of Fortacin from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription" in

[1] American Urological Association. Premature Ejaculation. Guideline on the Pharmacologic Management of Premature Ejaculation 2010

the EU.

In support of this change, the MAH provided an overview of the rationale of the request, including current treatment options for PE and summary data on Fortacin, as well as the reasons why they consider the criteria for classifying the product as subject to a medical prescription no longer apply to this product[2,3].

The submitted data and the four criteria mentioned in Article 71 of Directive 2001/83/EC and the European Commission Guideline on changing the classification for the supply of a medicinal product for human use have been considered by the CHMP during the assessment of the variation.

1. Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision

In (pre)clinical studies and post-marketing experience, Fortacin has shown a good safety profile with only a low incidence of mild-to-moderate drug related side effects.

No new information has become available regarding the toxicity profile of Fortacin and it is considered that Fortacin has a low general toxicity and no relevant productive toxicity, genotoxic or carcinogenic properties. The pre-clinical section of the summary of product characteristics (SmPC) is considered up to date and no changes are proposed.

One case of rash in one male patient was reported with positive dechallenge and rechallenge. Although the adverse event (AE) was non-serious and not-medically significant, CHMP considered that a warning on rash and skin irritation should be included in the product information, therefore section 4.4 of the SmPC and section 2 of the package leaflet are updated accordingly. No new adverse drug reaction (ADR) is proposed to be listed in the product information. Overall, CHMP considered that Fortacin has low risk of serious adverse reactions in the general population.

Due to the low systemic exposure to lidocaine and prilocaine and the short duration of its effect, systemic adverse reactions and drug-drug interaction (DDI) are not expected. No cases of DDI interactions have been reported and it is considered that the product information contains the appropriate information about any potential DDI to healthcare professionals and patients.

Deterioration has been observed when Fortacin is used with polyurethane-based female and male condoms. Therefore, Fortacin should not be used with polyurethane-based female and male condoms as protection from sexual transmitted diseases or pregnancy may be reduced. Fortacin can be used with contraceptive devices made of latex rubber, polyisoprene, nitrile and silicone as no deterioration has been shown with these materials. CHMP considers that this risk is manageable in a non-prescription setting and appropriate information and instructions have been included in the section 4.4 of the SmPC, section 2 of the package leaflet and the outer package for patients and physicians.

Precautionary measures are included in the product information for sexual partners and pregnant women recommending avoiding its use with pregnant or breast-feeding partners. The tabulated list of ADRs is updated to replace 'female' partners by 'sexual' partners.

With regard to the absence of indirect danger, CHMP agrees that the risk of hiding an underlying condition by a symptomatic improvement of PE with Fortacin is low in patient with primary PE. In patients with secondary (acquired) PE, other conditions could be present, such as ED or prostatitis and patients are able to identify other symptoms related to the disease. Unlike ED, that has been

[2] EC guideline 'Guideline on changing the classification for the supply of a medicinal product for human use' (Revision January 2006)
[3] CHMP guideline 'Guideline on legal status for the supply to the patient of centrally authorised medicinal products' (EMEA/186279/2006)

considered an early marker of cardiovascular disease, underlying conditions are not described to be associated to PE. Nevertheless, for precautionary measures, the section 4.4 of the SmPC and section 2 of the package leaflet are updated to state the if this product used as directed does not provide relief, the patient should discontinue its use and seek medical advice.

CHMP agrees with the MAH that the condition of PE can be easily assessed by the patient. In this context, Fortacin could benefit from a non-prescription status, as the accessibility to the drug will be easier.

The list of contraindications and warnings in the product information is very limited. The CHMP considers that the contra-indications, interactions, warnings and precautions are correctly reflected in the product information and can be easily understood by the patient.

Overall, CHMP considers that appropriate preventive actions are included in the SmPC, package leaflet and labelling of Fortacin with respect to the direct and indirect dangers, including how to use the product correctly, to prevent overdose or inadvertent trauma.

In view of the current safety profile of lidocaine/prilocaine containing medicinal products, it is unlikely that Fortacin will present a danger either directly or indirectly if utilised without medical supervision. This is also supported by the current safety knowledge on other similar products available as non-prescription medicines in some EU countries. CHMP concluded that criterion 1 does not apply to Fortacin.

2. Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health

There has been no report of incorrect use of Fortacin, or adverse reaction caused by overdose or excessive use. Neither have any adverse reactions been reported that have been caused due to non-adherence to the contraindications, precautions or warnings.

Although no risk of abuse or misuse have been identified with Fortacin or other prilocaine-lidocaine containing medicinal product, the use of Fortacin with recreational purposes with or without other drugs that enhance sexual performance cannot be ruled out if available as a non-prescription drug. The risk of off-label use will be followed in the next PSURs.

In addition, a statement reinforcing the fact that this medicine should not be used in children or adolescents is added to the package leaflet and in the outer packaging.

Based on the above, CHMP considered that Fortacin is unlikely to be frequently and to a very wide extent used incorrectly in a non-prescription setting, as a result are unlikely to present a direct or indirect danger to human health. CHMP concluded that criterion 2 does not apply to Fortacin.

3. Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation

With this variation the MAH does not apply for a new strength, dose, route of administration, therapeutic indication or new age group.

Although the post-marketing experience with Fortacin is still limited, the available post-marketing safety data are reassuring with only few non serious ADRs reported with Fortacin. Furthermore, lidocaine and prilocaine are well known active substances which are authorised worldwide in various topical formulations, including creams, sprays, gels and solutions, and also available as non-prescription medicines in some countries[4]. Two recent meta-analyses have reinforced the positive

[4] Waldinger MD. Drug treatment options for premature ejaculation. Expert Opin Pharmacother. 2018; 19 (10):1077-1085

benefit and safety profile of topical anaesthetics when used for PE[5,6].

Therefore, Fortacin does not contain any substances or preparations thereof, the activity and/or side effects of which require further investigation. CHMP concluded that criterion 3 does not apply.

4. Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection)

Fortacin is for cutaneous use and therefore not to be administered parentally (for injection). The fourth criterion does not apply to Fortacin.

5. Other considerations

Fortacin is included in a spray container. There are two containers authorised, one of 5 ml and one of 6.5 ml, which deliver 12 or 20 doses respectively. One dose is equal to 3 actuations. The maximum daily dose is 3 doses with at least 4 hours between doses. The product information advises patients to discontinue use and seek medical advice if the product used as directed does not provide relief. CHMP considers that appropriate instructions and precaution for use are included in the product information for patients and that the spray containers are adequate for use without medical prescription.

In conclusion, the CHMP considered that the four criteria mentioned in the European Commission Guideline on changing the classification for the supply of a medicinal product for human use do not apply to Fortacin and therefore the change from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription" is approvable. The SmPC, labelling and package leaflet are updated accordingly. In addition, the product information is updated in line with the latest QRD template (version 10.1). This includes the removal of a statement about *in vitro* interaction studies in section 4.5 of the SmPC as the absence of *in vitro* interactions which should not be mentioned. The benefit-risk balance of Fortacin remains unchanged.

With this variation the RMP (version 4.0) is updated in line with the version 2 of the GVP module V.

In addition, the MAH should address the following issues in the next PSUR:

Due to the still limited experience with Fortacin, in order to promptly assess the safety data when the product becomes a non-prescription medicine, the PSUR frequency should be changed from 3-year to a 2-year cycle to allow the collection of timely information. In addition, in the next PSURs, potential risks that may arise are requested to be followed (Methaheamoglobinemia, Hypersensitivity, Effect on fertility, Partner exposure (including ADRs reported from the partner), Pregnancy cases, incorrect and off-label use).

Furthermore, the Committee considers that this variation implements changes to the decision granting the marketing authorisation due to a significant public health concern on the following grounds:

This variation changes the legal status of the medicinal product, as discussed in section 3 below.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.5.b	C.I.5.b - Change in the legal status of a medicinal	Type II	I, II, IIIA

[5] Xia JD, Han YF, Zhou LH, et al. Efficacy and safety of local anaesthetics for premature ejaculation: a systematic review and meta-analysis. Asian J Androl. 2013;15 (4) :497–502
[6] Pu C, Yang L, Liu L, et al. Topical anesthetic agents for premature ejaculation: a systematic review and meta-analysis. Urology. 2013;81:799–804

Variation requested		Type	Annexes affected
	product for centrally authorised products - All other legal status changes		and IIIB

Change in the legal status of Fortacin from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription'. As a consequence, sections 4.4, 4.8, 4.9 of the SmPC are updated. The package leaflet and labelling are updated accordingly. Furthermore, the product information is being brought in line with the latest QRD template (version 10.1). The RMP is updated to version 4.0.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Fortacin-H-C-2693-II-0030'

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Fortacin containing the active substances lidocaine (150 mg) and prilocaine (50 mg) is a cutaneous spray solution for application to the glans penis indicated in the treatment of primary premature ejaculation (PE) in adult men. It was approved in the European Union (EU) on 15 November 2013.

PE is a prevalent male sexual disorder and causes a high level of bother and distress. It has been classified into two forms: a primary (lifelong) form that begins when a male first becomes sexually active and a secondary (acquired) form. Pharmacotherapy is the basis of treatment in life-long PE. In acquired PE, it is recommended to treat also the associated condition, such as erectile dysfunction or prostatitis. The negative consequences of long-term and unsuccessfully treated PE, on both patient and partner, are well established in the literature and include personal distress, impairment of the partner's sexual function, and interpersonal difficulties (Porst, 2019)[7].

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.

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.

In the present application, the MAH is requesting a change in the classification for the supply of Fortacin in the European Union from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription".

In support of this change, the MAH provided an overview of the rationale of the request, including current treatment options for PE and summary data on Fortacin, as well as the reasons why they consider the criteria for classifying the product as subject to a medical prescription no longer apply to this product. A summary of clinical efficacy and safety is also provided.

6. Clinical Efficacy aspects

At the time of approval, 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 ejaculatory latency time (IELT) ≤ 1 minute 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 Lidocaine/Prilocaine Plethora-treated subjects and 18.8% of placebo-treated subjects

[7] Porst H, Burri A. Novel Treatment for Premature Ejaculation in the Light of Currently Used Therapies: A Review. Sex Med Rev. 2019; 7(1):129-140

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 ($p < 0.0001$).

7. Clinical Safety aspects

Clinical development

No major safety concerns were identified in the clinical development of Fortacin for PE at the time of approval.

Most of adverse events reported were mild or moderate in intensity and mainly localised reactions related to the local administration and mechanism of action of the product (genital hypoaesthesia, erectile dysfunction, genital burning sensation, genital erythema and ejaculation failure).

Few cases were considered severe (3 cases of ED, impaired glucose tolerance, hypercholesterolaemia, hyperlipidaemia and hypertension) all of them considered related to the studied medicinal product. Some systemic adverse events were also observed such as nasopharyngitis, headache and influenza.

Overall, the female sexual partners also had treatment emergent adverse events (TEAEs), some localised and related to the local administration of the product (vulvovaginal burning sensation, vulvovaginal discomfort and hypoaesthesia) and other systemic (headache, influenza, nasopharyngitis). There is no data in male sexual partners although no differences regarding adverse events in genital mucosa are to be expected.

Furthermore, it is known that the use of prilocaine in high doses may cause an increase in the methaemoglobinaemia level particularly in conjunction with methaemoglobinaemia-inducing agents (e.g. sulphonamides). In addition, there is carcinogenicity potential from o-toluidine metabolite in humans, a prolonged exposure could lead to a higher incidence of these potentially negative events. The potential occurrence of these risks seems to be negligible although cannot be ruled out. A specific wording is included to reflect these risks in the section 4.9 and 5.3 of the SmPC respectively and the risk management plan (RMP). Similarly, a concern related to the potential risks for the foetus in pregnant women was also raised. Given the limited data available, some recommendations are provided in the product information.

Post-marketing data

Fortacin was first launched in the UK in November 2016; to date, it has also been launched in Italy,

France, Spain, Germany and in Portugal in 2018.

A cumulative patient exposure of 58,431 patients (data lock point (DLP) = 15 May 2019) has been estimated from the number of cutaneous spray solution packet units sold (1 pack corresponds to 1 patient). However, the units sold probably do not correspond to the exact number of patients exposed and may reflect overestimation.

Cumulatively, only 5 non serious Individual Case Safety Reports ICSRs have been collected from post-marketing sources since the launch of the product: two of these reports were "drug ineffective", the other three ICSRs were one report of genital burning sensation in a female partner, one report of genital blister and one report of rash each experienced by separate male patients. The outcome of these events is "unknown" for genital blister, and "recovered" for genital burning sensation and rash (see additional information in section 8 of the report: criterion 3). Genital burning sensation is listed as adverse reactions in the current Fortacin SmPC. A warning about rash is proposed to be added in the product information.

During the reporting period, a qualitative market research has been conducted in Italy with the objective to better understand the condition of the patients with PE, and their perception and experience with the different products available on the market, with a focus on Fortacin. In this research, a total of 28 solicited ICSR have been collected, including 21 cases of product misuse due to underdosing. The following non serious adverse reaction have been reported: genital hypaesthesia (3), penile burning sensation (2), vulvovaginal burning sensation (2), not better specified off-label use (1), effect decreased (1).

No serious adverse reactions were collected, and no new safety signal has been identified from these reports.

8. Analysis of Fortacin 150 mg/mL + 50 mg/mL cutaneous spray with respect to the four criteria of the EC Guideline

According to the "EU Guideline on changing the classification for the supply of a medicinal product for human use, Rev. January 2006", a number of criteria should be taken into consideration for classifying a medicinal product as not subject to medical prescription.

These four criteria are:

1. Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision
2. Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health
3. Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation
4. Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection)

Criterion 1: Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision

A summary of the MAH's justification for the first criterion is provided below.

1.1 Direct danger/safety profile

a) Toxicity

The plasma levels of lidocaine and prilocaine in male and female subjects exposed to Fortacin are well below the levels associated with human toxicity (5000 ng/mL). After repeated dosing, 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 level. Female volunteers receiving repeated doses 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.

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.

Use in 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. 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. As per the SmPC, 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.

Lidocaine and prilocaine are excreted in human milk, but at therapeutic doses of Fortacin no effects on the breastfed new-borns/infants are anticipated due to active substance transfer from the male patient to his female partner. This is also reflected in the SmPC of Fortacin.

No effects of reproductive toxicity have been reported in the clinical development of Fortacin or the post-marketing experience to date. However, the MAH acknowledges that the exposure of pregnant women to Fortacin is limited. There was only one incident of pregnancy during the clinical development of Fortacin and no information on the outcome was obtained. Suitable warnings are provided for the patient in the Package Leaflet and there has been no report of pregnancy since the product was launched.

Despite the fact that lidocaine and prilocaine both rapidly cross the placenta, the limited systemic absorption of lidocaine and prilocaine from Fortacin would mean that drug concentrations in the placenta and foetus would be correspondingly low, so that it is not considered likely that the drug will cause any reproductive toxicity should a pregnant woman be exposed. Reports of adverse effects of lidocaine or prilocaine on the foetus have not been located in the literature despite their use for many years.

As a precautionary measure, it is reported in the current product information that 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.

Effect on fertility

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 cannot be excluded; therefore it is not possible to state whether Fortacin would prevent pregnancy. Overall, the MAH does not considered that there will be any increase in the incidence of reproductive toxicity or effect on fertility due to the change in classification of Fortacin to non-prescription, as proposed.

Genotoxicity and carcinogenicity

Lidocaine

Lidocaine was not genotoxic and the carcinogenic potential of lidocaine has not been studied. The lidocaine metabolite 2,6-xylidine has genotoxic potential *in vitro*. In a carcinogenicity study of rats exposed to 2,6-xylidine 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 the minimum dose studied. Note, this dose did result in tumours.

The MAH do not consider that the risks of genotoxicity or carcinogenicity would be increased due to the change in classification of Fortacin to non-prescription, as proposed and it would be no greater for Fortacin than any of the other similar products currently classified as non-prescription.

b) Interactions

Topical drugs

The results of *in vitro* studies showed that there was no interference by Fortacin with topical antifungal (clotrimazole, econazole, imidazole, nystatin, miconazole, ketoconazole), antibacterial (clindamycin, metronidazole) and antiviral medicinal products (acyclovir).

Other drugs

The low systemic exposure to lidocaine and prilocaine and short duration of topical application means that drug-drug interactions of clinical significance are considered to be unlikely.

The following interactions are considered for all topical products containing lidocaine and prilocaine and are included in the SmPC:

- Prilocaine at high doses may cause an increase in methaemoglobin levels, particularly in conjunction with methaemoglobin- inducing medicinal products. As consequence, methaemoglobinaemia may be accentuated in patients already taking medicinal products known to induce the condition, e.g. sulphonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, metoclopramide, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenobarbital, phenytoin, primaquine and quinine
- The risk of additional systemic toxicity should be considered when large doses of local anaesthetics are applied to patients already using other local anaesthetics or medicinal products 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.
- Medicinal products that reduce the clearance of lidocaine (e.g. cimetidine or betablockers) might cause potentially toxic plasma concentrations when lidocaine is given intravenously in repeated high doses over a long time period (30 hours).

There have been no reports of drug-drug interactions with Fortacin. Information on the above risks is included in the SmPC and the Package Leaflet (see Section 2 'Warning and precautions). The risk of systemic exposure leading to systemic reactions e.g. methaemoglobinaemia was included as an "important potential risk" in the RMP (version 3.1) submitted at time of this variation, as it is acknowledged that prilocaine is the local anaesthetic most commonly associated with this condition. However, as the absorption area in the clinical use of Fortacin is very small, and the absorption so low, the risk of methaemoglobinaemia is considered to be extremely unlikely even with the change in classification of Fortacin to non-prescription, as proposed. This risk has been removed from the safety concerns of the RMP (version 4) and will be followed in the PSURs.

Drug-device interaction

Device interaction testing conducted with barrier contraceptives showed that the tensile strength of polyurethane devices (female and male condoms) was compromised, causing increased puncture rates. Devices made from latex rubber, polyisoprene, nitrile and silicone were unaffected.

Any barrier contraceptives (e.g. male or female condom) which are made from polyurethane based material cannot guarantee to protect against disease or pregnancy.

This is considered an important potential risk in the RMP (version 3.1) submitted at time of this variation. Appropriate information is proposed to be included in the Product Information. There have been no reports of such an interaction since the product was launched. This risk has been removed from the safety concerns of the RMP (version 4).

c) Adverse reactions

Risk of serious type A reactions[8] in the general population

In all studies, Fortacin has shown a good safety profile with only a low incidence of mild to-moderate drug-related side effects, as demonstrated in a combined evaluation of 596 male patients and 584 female partners who participated in the clinical trials. Most treatment-related side effects occurred immediately or within 24 hours of treatment and most were mild or moderate in severity. None were serious.

[8] Type A: Those that result from exaggeration of a medicinal product's expected pharmacological actions when given in the usual therapeutic dose; normally dose-dependent.

The most frequent side effects reported in male subjects were local effects of genital hypoesthesia (4.5%) and ED (4.4%), with discontinuation of treatment in 0.2% and 0.5% of subjects, respectively. The most frequent side effects reported in female partners were vulvovaginal burning sensation (3.9%), and genital hypoesthesia (1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects.

Erectile dysfunction was included in the RMP (version 3.1) as an "important identified risk", as it is acknowledged that Fortacin could affect nerve endings in the penis and aggravate the condition. In the clinical development program all reports of ED resolved without treatment and there have been no reports of ED since the product was launched. If this adverse reaction was to occur, any effect would be short-lived due to the duration of action of lidocaine and prilocaine. Erectile dysfunction should therefore be considered an undesirable effect (already included in the product information), but not a true safety concern. This risk has been removed from the safety concerns of the RMP (version 4).

Inadvertent trauma, secondary to hypoaesthesia, was included as an "important potential risk" in the RMP (version 3.1) submitted at time of this variation. In the clinical development programme all male subjects and female partners recovered from hypoaesthesia without treatment. There were no recorded cases of trauma occurring as a result of genital (or other area) hypoaesthesia and there have been no confirmed reports since the product was launched. Suitable warnings on the risks associated with hypoaesthesia are already included in the Package Leaflet (see Section 2 'Warnings and precautions'). This risk has been removed from the safety concerns of the RMP (version 4).Exposure via partner leading to application site reactions and trauma secondary to hyopaesthesia was included as an "important potential risk" in the RMP (version 3.1) submitted at time of this variation. In clinical trials, all female partners recovered from these reactions without treatment and there has only been one report of a localised adverse reaction due to partner exposure since Fortacin was launched. This risk has been removed from the safety concerns of the RMP (version 4).

In the post-marketing experience only a few, non-serious adverse reactions have been reported and no new safety signal has been identified.

In total, 8 ADRs in 5 ICSRs were reported from spontaneous sources and 28 ICSRs from a qualitative market research study. The ICSR are in line with the labelled safety profile of Fortacin except from a non-serious adverse drug reaction of local rash. The time to onset in unknown, the AE lasted 5 days and the patient recovered. Although the case reported a positive dechallenge and rechallenge, with the information available, it is not possible to determine if it is secondary to a local administration or if it is a hypersensitivity symptom.

No serious risk has been identified when Fortacin is used in real life conditions. Furthermore, no serious risk has been identified for other similar products which are supplied on a non-prescription basis.

The MAH, therefore, do not consider that the risk of serious Type A reactions to Fortacin will increase due to the change in classification to non-prescription, as proposed.

Risk of serious type B reactions[9]

The active substances are well established and are widely used in different dosage forms, including various topical non-prescription preparations, as detailed above. Allergic reactions to the amide group of local anaesthetics are only rarely reported. However, it is acknowledged that such reactions can be life-threatening. There have been no reports of hypersensitivity to Fortacin.

As per the SmPC, in order to avoid hypersensitivity reactions, Fortacin should not be used in patients or their partner with a known history of sensitivity to local anaesthetics. The Package Leaflet contains

[9] Type B: Those that represent a novel response not expected from known pharmacological action.

information that Fortacin is contraindicated in patients, or their partners, with hypersensitivity to any of the ingredients in Fortacin or to local anaesthetics of the amide type.

The MAH, therefore, considered that the risk of serious Type B reactions to Fortacin will be any greater than any of the other similar products currently classified as non-prescription medicine.

d) Preventive actions

Detailed information for the user is contained in the Package Leaflet of Fortacin with respect to the direct and indirect dangers, including how to use the product correctly, to prevent overdose, or inadvertent trauma. This is considered to represent adequate routine risk minimisation activities by the MAH; notably, there have been only isolated local adverse reactions reported since the product was launched with no new safety signals.

e) Safety vs other treatment

The adverse reactions reported with the use of Fortacin in male patients or in female partners are mainly local effects, mostly classed as mild or moderate as per Fortacin's SmPC. Only a few local adverse reactions have been reported since the product launch. Similarly, the most frequently observed adverse drug reactions observed with EMLA 5% (lidocaine/prilocaine), a topical anaesthesia, are related to administration site conditions (transient local reactions at the application site) (EMLA SmPC).

On the contrary, syncope and orthostatic hypotension have been reported in clinical trials with dapoxetine hydrochloride, a short-acting SSRI (Priligy SmPC) indicated for the treatment of PE in adult men. The following adverse drug reactions were most commonly reported during Phase 3 clinical trials and were dose related: nausea (11.0% and 22.2% in 30 mg and 60 mg prn dapoxetine groups, respectively), dizziness (5.8% and 10.9%), headache (5.6% and 8.8%), diarrhoea (3.5% and 6.9%), insomnia (2.1% and 3.9%) and fatigue (2.0% and 4.1%). The most common adverse events leading to discontinuation were nausea (2.2% of Priligy-treated subjects) and dizziness (1.2% of Priligy-treated subjects).

Of note, other SSRIs are used off-label as oral daily treatment of PE, exposing the patients to systemic side effects (Waldinger, 2004)[10].

1.2 Indirect danger/ safety profile

The MAH considers that there is no risk to hide an underlying condition by a symptomatic improvement of PE with Fortacin. In patients with primary PE no underlying condition is present.

In case of use also in patients with secondary (acquired) PE, other conditions could be present, such as erectile dysfunction or a prostatitis. Since these conditions should be also treated, the Package Leaflet is proposed to be amended in order to avoid the long-term use of Fortacin without consulting a physician.

The MAH considers that a wider use of Fortacin would not increase the risk of resistance to the product in the general population.

1.3 Self-assessment

The MAH considers that the condition of PE can be easily assessed by the patient.

Patients with primary PE ejaculate too early at almost every attempt at intercourse, with (nearly) every sexual partner. A physical examination is not mandatory. Self-estimation by the patient and

[10] Waldinger MD. Drug treatment options for premature ejaculation. Expert Opin Pharmacother. 2018 Jul;19(10):1077-1085.

partner of the ejaculatory latency is accepted as the method for determining IELT in clinical practice. There is no risk of over diagnose the condition by the patient.

The MAH also considers that the availability of a non-prescription product for PE, specifically designed and developed to treat this condition, would be important, and would avoid the off-label use of other medicines available without medical prescription. Although premature ejaculation is a common male sexual dysfunction, patients are often unwilling to discuss their symptoms with doctor and use products subject to non-prescription.

1.4 Risk and consequences of incorrect use

There have been no reports of incorrect use of Fortacin, or adverse reactions caused by overdose or excessive use. Neither have any adverse reactions been reported that have been caused due to non-adherence to the contraindications, precautions or warnings.

The MAH considers that overdose of lidocaine or prilocaine with Fortacin is unlikely due to the small container size and low systemic availability of the active ingredients following topical application. Furthermore, overdose due to excess application is extremely unlikely.

The MAH considers that there are clear instructions on "How to use Fortacin" included in Section 3 of the Package Leaflet, as well as actions to take if it is considered that too much Fortacin has been applied.

1.5 Patient information

The MAH has revised different sections of the product information to a non-prescription setting in order to provide necessary guidance to men, while minimising risk for them and their sexual partners. It also includes appropriate instructions as to when the patient should consider consulting Doctor or Pharmacist, including when they suspect that they have had an adverse reaction to the product.

The MAH considers that since the product is for self-use by the patient for PE, it is unlikely that the way in which the medicinal product will be used as an drug subject to non-prescrition will differ from the way in which the same product has been used when available as prescription drug. Notably, there are several other similar products, which are currently available as medicines subject to non-prescription.

The MAH also stated that the current product information has undergone User Testing during the MAA procedure to ensure that they convey the required information to patients in a format and style that is easy to access and understand. It should also be noted that the information is similar to what is included for other local anaesthetics available as products subject to non-prescription.

CHMP discussion on first criterion

First criterion: Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision

The CHMP has considered the safety profile of Fortacin in order to ensure that it is not likely to present **a direct danger** even when used correctly, if utilised without medical supervision.

The plasma levels of lidocaine and prilocaine in male and female subjects exposed to Fortacin are well below the levels associated with human toxicity (5000 ng/mL). After repeated dosing, 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 level. Female volunteers receiving repeated doses 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.

The MAH has also provided some comparisons of the plasma concentrations of Fortacin following 3 applications of Fortacin at 4-hourly intervals in one day to volunteer males (the maximum dose recommended in the SmPC) and EMLA Cream after the application of 10 g for 10 minutes to vaginal mucosa. While for lidocaine similar systemic concentrations are achieved for prilocaine such exposure was 10-fold below for Fortacin. The limited contribution of prilocaine to any potential systemic AE is reassuring. Nevertheless, such systemic concentrations could increase if greater amounts of Fortacin were used and potential consequences both at local and systemic level cannot be ruled out. The dose recommended in the SmPC is 3 actuations to cover the glans penis. A maximum of 3 doses can be used within 24 hours with at least 4 hours between doses is specified in the product information. However, since a more extensive use of Fortacin is possible the recommendation for not exceeding the recommended posology (3 doses within 24 hours) has been reinforced in the package leaflet and the outer package.

No new information has become available regarding the toxicity profile of Fortacin and it is considered that Fortacin has a low general toxicity and no relevant productive toxicity, genotoxic or carcinogenic properties. The pre-clinical section of the product information is considered up to date.

The safety profile of Fortacin for both male glans-penis-treated subjects and female partners appears to be benign and manageable since adverse events observed during the clinical trials seem to be expected considering the mechanism of action of both anaesthetics (lidocaine and prilocaine) and the topical administration of this cutaneous solution.

With regard to the post-marketing experience with Fortacin, which is still limited, no new safety concerns have been identified except a case of rash in one male patient. Although the case reported a positive dechallenge and rechallenge, with the information available, the reported adverse drug reaction is not systemic and does not represent a safety issue since it is non-serious and not-medically significant. However, CHMP recommends including a warning on rash and skin irritation in section 4.4 of the SmPC, in the package leaflet. No new ADR is proposed to be listed in the product information. The tabulated list of ADRs is now updated to replace 'female' partners by 'sexual' partners.

Overall, CHMP considered that Fortacin has low risk of serious adverse reactions in the general population.

Due to the low systemic exposure to lidocaine and prilocaine and the short duration of its effect, clinically relevant drug-drug interactions (DDI) are not expected. *In vitro* DDI studies with products that are more likely to be concomitantly given, like topical antifungal, antibacterial and antiviral, have not shown loss of antimicrobial activity. No concerns related to DDI interactions are in principle foreseen. No changes to the product information regarding the interactions are considered necessary.

There are limited data about the impact of Fortacin on women of childbearing potential, pregnancy and lactation. Even when it is not indicated for women there may be some exposure in female partners and that is why precautionary measures are included in the product information recommending avoiding its use in pregnant sexual partners. Furthermore, CHMP considers that these recommendations should be reinforced in the package leaflet (section 2) to state that Fortacin should not be used whilst the partner is pregnant unless an effective male condom is used.

Deterioration has been observed when Fortacin is used with polyurethane-based female and male condoms. Patients/partners who want to use a condom should check that it is polyurethane free and Fortacin must not be used with polyurethane-based female and male condoms as deterioration was observed and protection from disease or pregnancy may be reduced. Fortacin can be used with

contraceptive devices made of latex rubber, polyisoprene, nitrile and silicone as no deterioration has been shown with these materials. The section 4.4 of the SmPC, the section 2 of the package leaflet and the outer packaging are updated to reflect this warning.

CHMP considers that appropriate preventive actions are included in the SmPC, package leaflet and labelling of Fortacin with respect to the direct and indirect dangers, including how to use the product correctly, to prevent overdose, or inadvertent trauma. This is considered to represent adequate routine risk minimisation activities.

Based on this safety profile, CHMP considered that Fortacin is not likely to present a direct danger even when used correctly, if utilised without medical prescription.

With regard to the **absence of indirect danger**, CHMP agrees that the risk of hiding an underlying condition by a symptomatic improvement of PE with Fortacin is low in patient with primary PE. In patients with secondary (acquired) PE, other conditions could be present, such as ED or prostatis. The product information is updated to reflect that if the product used as directed does not provide relief, the patient should discontinue its use and seek medical advice.

CHMP considered the **self-assessment of the condition** by patient as follows.

PE is defined according to three essential criteria: (i) brief ejaculatory latency; (ii) loss of control; and (iii) psychological distress in the patients and/or partner. The three criteria can easily be identified by the patient itself and that is why PE is usually a self-reported diagnosis. Unlike erectile dysfunction, that has been considered an early marker of cardiovascular disease, underlying conditions are not described to be associated to primary PE. In this context, Fortacin could benefit from a non-prescription status, as the accessibility to the drug will be easier.

Furthermore, CHMP considered that the contra-indications, interactions, warnings and precautions are correctly reflected in the product information and can be easily understood by the patient.

With regard to the **risk and consequences of an incorrect use**, CHMP considers that the list of contraindications and warnings in the SmPC is very limited so if Fortacin is used as an non-prescription medicine the incidence and risk of misuse is not expected to be increased.

It acknowledged that the use of Fortacin in a non-prescription setting could not be limited to primary PE. However, it is likely that patients with PE secondary to prostatitis or erectile dysfunction (the most frequent causes of secondary PE) are able to identify other symptoms related to the disease. Prostatitis is usually accompanied by other symptoms like pain, voiding, general symptoms (like fatigue, malaise, fever) that makes patients to seek medical attention. Similarly, erectile dysfunction can also be identified by the patients. The potential for misuse in these specific situations seems low. Nevertheless, the product information is updated to state that 'premature ejaculation may be due to a condition requiring medical supervision. If this product used as directed does not provide relief, the patient should discontinue use and seek medical advice'.

Regarding the **appropriateness of the product information**, it is not expected that the use of the product represents a concern if administered without medical supervision. In addition to the package leaflet, appropriate, instructions on use have been included in the labelling. These include the indication and age limit, the posology and maximum daily dose, warnings about avoiding contact with eyes, nose, mouth and ears, and recommendation not to use Fortacin with polyurethane condoms. CHMP considers that this information is sufficient to substitute for the absence of medical supervision. The package leaflet also advises to always use Fortacin exactly as described in the leaflet or as the physician or the pharmacist have instructed. In addition, the section 4.4 of the SmPC and section 2 of package leaflet also informs that patient that PE may be due to a condition requiring medical

supervision and that if the product used as directed does not provide relief, the patient should consult a doctor.

Contraindications, interactions, warnings and precautions (such as related to the contact of Fortacin with eyes, mouth, other mucous membranes and use of condoms) are clearly described in layman's terms and prominently presented in the leaflet. The results of the user consultation with target patient groups on the package leaflet submitted by the MAH during the evaluation show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

In order to monitor potential risk that may arise due to the change of legal status, CHMP requests that the following issues be monitored in the next PSUR: Methaemoglobinemia, Hypersensitivity, Effect on fertility, Partner exposure (including ADRs reported from the partner), Pregnancy cases, Incorrect use, and Off-label use.

CHMP conclusion on the first criterion

In view of the above discussion, the CHMP considered that Criterion 1 of the Article 71 of Directive 2001/83/EC and European Commission Guideline "Medicinal products shall be subject to medical Table of Contents EMA/73099/2015 Page 30/76 prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision" does not apply.

Criterion 2: Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

The following justification has been provided by the MAH for the second criterion.

According to the MAH, there is no risk of abuse use in unapproved indications, since local anaesthetics are not associated with recreational use.

There is no evidence that Fortacin is used incorrectly either frequently, or to a widespread extent, causing a direct or indirect danger to human health.

No case of drug abuse or incorrect use has been reported for Fortacin during its administration during the clinical development and during post-marketing experience.

The literature reports reviewed on other non-prescription products containing local anaesthetics have not indicated any risk of incorrect use.

Following request by CHMP during the procedure due to concerns on the risk of misuse in a recreational intention, the MAHs could not find any cases concerning the risk of misuse "recreational intention to prolong sexual performance" in EVDAS for Fortacin, EMLA and other similar products.

In addition, following a search on websites of the MHRA, CMDh, FDA and EMA and a review relevant to all safety report concerning the preferred 'term misuse' and 'off-label use', the MAH did not identify any potential safety signal on potential misuse and off-label used relevant to lidocaine as single active ingredient with similar indication granted to Fortacin.

On the basis of the safety data review concerning the extraction via EVDAS of all misuse safety reports and related PTs, there is no evidence that the safety profile of lidocaine prilocaine containing products such as EMLA (and other similar products) could be influenced by the use "with recreational intention to prolong sexual performance". The MAH will ensure the continuous product safety monitoring throughout routine pharmacovigilance activities such as close monitoring and review in PSURs and signal management activities.

The MAH considers that the proposed change of the classification of Fortacin to non-prescription, is not considered to pose an additional risk of undesirable effects and untoward occurrences which would adversely affect the product's positive benefit-risk profile.

CHMP discussion on the second criterion

Second Criterion: Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

According to the MAH, there is no risk of abuse or misuse of Fortacin in unapproved indications since local anaesthetics are not associated with recreational use and no safety signal of misuse and off-label use have been identified with other prilocaine-lidocaine containing medicinal products.

CHMP noted the above information but considers that the potential use of Fortacin with or without other drugs that enhance sexual performance cannot be ruled out, if available as a non-prescription drug. The safety profile of Fortacin seems relatively benign when used for the treatment of PE, although data available in the post-authorisation setting is scarce.

Due to the still limited experience with Fortacin, in order to promptly assess the safety data when the product becomes a non-prescription medicine, the PSUR frequency should be changed from 3-year to a 2-year cycle to allow the collection of timely information. The risk of off-label use should be followed in the next PSURs.

In addition, it is important to consider the access of the children to the medicine. The Guideline, as other consideration, states that the container should as far as possible prevent children gaining access to the medicine. A statement reinforcing the fact that this medicine should not be used in children or adolescents under 18 years of age is added in section 2 of the package leaflet. In addition, the outer packaging will include a warning stating "keep out of the sight and reach of children".

CHMP conclusion on second criterion

In view of the above discussion, the CHMP considered that Criterion 2 of the Article 71 of Directive 2001/83/EC and European Commission Guideline "Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health" does not apply.

Criterion 3: Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation.

A summary of the justification provided by the MAH for the third criterion is provided hereafter.

The MAH considers that Fortacin does not contain any substances or preparations thereof, the activity and/or side effects of which require further investigation based on the following data.

3.1 Recent authorisation/limited experience

In the EU, a centralised MA for Fortacin was granted on 15 November 2013 (international birth date). Even considering that the post-marketing experience with Fortacin has been for a limited period, only a few non serious ADRs have been reported so far.

Furthermore, an extensive post-marketing experience over a considerable number of years, supports the use of local anaesthetics as on demand treatment for PE.

Lidocaine and prilocaine are authorised worldwide in various topical formulations, including creams, sprays, gels and solutions, which are available as non-prescription medicines (Waldinger, 2018)4.

Two recent meta-analyses have confirmed the positive benefit-risk profile of topical anaesthetics when used for PE. They have a favourable side-effect profile. In general, a low incidence of topical side-effects occurs mainly of penile hypoaesthesia, numbness or erectile difficulties. Transfer of the cream to the female partner may lead to vaginal numbness. Analysis of eight trials has shown the efficacy and safety of topical anaesthetic treatment for lifelong PE (Xia 2013; Pu 2013)5,6.

Safety profile of similar products used for PE, currently supplied as non-prescription medicines

• EMLA Cream

EMLA Cream 5% is a eutectic mixture of lidocaine and prilocaine and is marketed as a non-prescription medicine in a number of EU countries. EMLA Cream contains 2.5% lidocaine w/w (25 mg/g) and 2.5% prilocaine (25 mg/g), and it is approved not only for topical anaesthesia of the skin, but also for topical anaesthesia of the genital mucosa, e.g. prior to superficial surgical procedures or infiltration anaesthesia in adults and adolescents ≥12 years (EMLA UK SmPC).

Of interest, EMLA has been used off-label to treat premature ejaculation for a period of decades and it is still used (IQVIA-SPM 2018).

The most commonly reported events (>1%) with the use of EMLA Cream on the skin or on the genital mucosa are local reactions at the administration site, such as burning sensation, pruritus, erythema, oedema, warmth and pallor. Application site paraesthesia (tingling) has been uncommonly reported after application on the genital mucosa.

Methaemoglobinaemia is a rare reaction, more frequently observed in connection with overdose in newborns and infants <1 year. Patients with defective glucose-6-phosphate dehydrogenase, hereditary or idiopathic methaemoglobinaemia are more susceptible to active-substance induced signs of methaemoglobinaemia.

Metabolites of lidocaine and prilocaine include anilines such as 2,6-xylidine and o-toluidine, respectively, which are toxic at high levels. Symptoms of aniline poisoning include methaemoglobinaemia, headache, paraesthesia, hyperalgesia, poly neuritis, cardiac arrhythmias, dizziness, hypotension, convulsion, muscle weakness, and/or digestive derangement.

Allergic reactions to the amide group of local anaesthetics are rare. Occasional reports of contact sensitivity to lidocaine have been reported, and cross reactivity between lidocaine and prilocaine has also been described (Curley 1986; Timmermans 2009)[11,12].

EMLA Cream is contraindicated in individuals with known drug sensitivity to amide-type local anaesthetics and it is not recommended in patients with methaemoglobinaemia (congenital or idiopathic). In addition, individuals with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methaemoglobinaemia.

• Stud100 Spray

Stud100 was introduced onto the market in 1970, and is the oldest topical anaesthetic spray still marketed as an OTC medicine for delaying ejaculation. Stud100 Spray contains 9.6% w/w lidocaine presented as a metered aerosol spray delivering a dose of 7.7 mg lidocaine base per actuation. The recommended dosage is three or more metered actuations with a maximum dose of eight actuations

[11] Curley RK, Macfarlane AW, King CM. Contact sensitivity to the amide anaesthetics lidocaine, prilocaine, and mepivacaine. Case report and review of the literature. Arch Dermatol. 1986;122(8):924-6
[12] Timmermans MW, Bruynzeel DP, Rustemeyer T. Allergic contact dermatitis from EMLA cream: concomitant sensitization to both local anesthetics lidocaine and prilocaine. J Dtsch Dermatol Ges. 2009;7(3):237-8

(62 mg lidocaine). The Product Information reports that, in extremely rare cases, local anaesthetic preparations have been associated with allergic reactions and that occasional local skin irritation may occur. It is also reported that the plasma lidocaine levels achieved following application of Stud100 at the maximum recommended dose are extremely low, at about 25 x lower than the concentrations associated with systemic toxicity (STUD 100 UK SmPC).

• Promescent spray

Promescent is a lidocaine spray in a metered-dose delivery system, which is currently available in the USA as an OTC medicine to delay ejaculation. Similar to Fortacin, Promescent also utilizes a eutectic formulation which enables increased absorption of the anaesthetics through the skin. Promescent and Fortacin deliver similar doses of anaesthetics per actuation; Promescent delivers 10 mg lidocaine and Fortacin delivers 7.5 mg lidocaine and 2.5 mg prilocaine per actuation.

In the Prescribing Information of Promescent it is reported that if the patient or his partner develop a rash or irritation, such as burning or itching, the product should be discontinued and, if symptoms persist, a Doctor should be consulted. It is also reported that if the product does not provide relief, the patient should discontinue its use and consult a Doctor (https://www.drugs.com/otc/120607/promescent.html).

• Dynamo Delay: Lidocaine USP 13% (approximately 10 mg per spray) and

• KY-Duration: Lidocaine USP (9.6%) (Approximately 10 mg per Spray)

These are both topical anaesthetic sprays for external use indicated in the treatment of PE and marketed in the USA as non-prescription products (https://www.drugs.com/otc/325841/dynamodelay.html). Both products have a similar safety profile to other OTC topical anaesthetic products and may cause local side effects such as rash or irritation and burning or itching. In case of allergy, products administration should be discontinued. As for other topical anaesthetics, contact with the eyes must be avoided.

Safety profile of other lidocaine-containing products for genital use

Other lidocaine-containing products for genital use are also currently marketed in EU as non-prescription medicines.

Vagisil 2% is marketed in Italy and UK without prescription, for the relief of intimate itching, burning and irritation and contains lidocaine base 2% w/w (20 mg/g): dose and posology consist of an appropriate quantity of cream, applied 3-4 times a day. If 3-5 g of cream are applied, per application, a single dose of 60-100 mg of lidocaine is administered with a maximum of 240-400 mg of lidocaine administered within 24 hours.

Luan 2.5 % gel (a product marketed in EU countries without prescription, to facilitate intra-urethral manoeuvres such as the introduction of catheters). The product contains lidocaine hydrochloride (25 mg/g), dose and the posology comprises application of 15 g gel in a single dose, corresponding to 375 mg of administered lidocaine.

Several other lidocaine-containing drugs are currently marketed in EU countries without prescription and are indicated for administration to the oral mucosa (e.g. spray for sore throat pain relief or gingival gel) or to the anal mucosa, for itching relief in the case of haemorrhoids (either in cream or suppositories).

3.2 New strength, dose, route of administration, indication, new age group or combination of substances

With this variation the MAH does not apply for a new strength, dose, route of administration, therapeutic indication or new age group.

CHMP discussion on third criteria

Third criterion 3: Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side-effects of which require further investigation.

With regard to **recent authorisation/limited experience**, CHMP acknowledges that there has been limited post-marketing experience due to the recent authorisation of Fortacin (2013) and recent launch of the product in few countries (from 2016 in UK, and from 2018 in Italy, France, Spain, Germany and Portugal).

According to the MAH, the cumulative exposure of the drug (until May 2019) ascended to 58,431 patients (estimated from the numbers of cutaneous spray, solution packet units sold, taking into account that 1 pack corresponds to 1 patient). It is important to highlight that the sales after starting marketing authorisation could reflect channel saturation (on stock by wholesalers or pharmacies) instead a real estimation of patient exposure. So, the number of patients exposed could be overestimated.

However, the post-marketing safety data is reassuring with cumulatively 8 ADRS in 5 ICSRs received and 28 ICSRs including 21 non serious cases of product misuse due to underdosing collected from a qualitative market research study in Italy. The following non-serious ADRs have also been reported: genital hypaesthesia (3), penile burning sensation (2), vulvovaginal burning sensation (2), not better specified off-label use (1), effect decreased (1).

The MAH has provided information on other products used for PE, currently supplied as non-prescription medicines (Stud100 Spray, Promescent spray, Dynamo Delay and KY Duration). The information included general data of all of them, and what the product information states for them.

At the request of CHMP, the MAH also conducted a research in order to retrieve any potential safety signal relevant to lidocaine as single active ingredient with similar indication granted to Fortacin. The results of this search did not highlight any potential safety signal. In addition, a review relevant to all safety reports concerning PT Misuse and Off-label use (along with related terms) has been done for products with similar composition (lidocaine prilocaine) through a Standardized MedDRA Query (SMQ) in the EVDAS.

Up to know, no relevant safety reports from these safety issues have been found for Fortacin. However, the change in the legal status may be related to the lack of posology compliance or not following the precautions of use and therefore, systemic exposure of lidocaine/prilocaine may occur in users but even more in their partners. In order to follow these potential risks, the PSUR frequency submission will be shortened to 2 years. The risk to expose patients and their partners to an inappropriate use of Fortacin should be lower in comparison to similar medicinal products due to its administration limited to topical application but not on large skin areas, and also its metered-dose spray that allow the delivery of limited quantities of product. However, misuse and potential ADRs that could emerge from the misuse and off-label use should be followed in the PSURs.

Furthermore, it is important to have post-marketing experience in the general population, including elderly, children etc. Regarding children, Fortacin is indicated in adult men but other products containing lidocaine/prilocaine, such as EMLA is authorised in paediatric population.

According to the MAH, two recent meta-analyses have confirmed the positive benefit-risk profile of topical anaesthetics when used for PE (Xia 2013; Pu 2013)5,6. In addition, there is another review with

similar conclusions (Butcher. et.al 2019)[13]: topical agents are an effective and well-tolerated option for treatment of PE; the topical agents have minimal systemic side effects including minimal partner absorption), allow for spontaneity with on demand usage and demonstrate effective delay of IELT.

CHMP agrees with the MAH that Fortacin does not constitute to a **new strength, dose, route of administration, indication, new age group or combination of substances**, and that this criterion does not apply.

CHMP conclusion on third criteria

In view of the above discussion, the CHMP considered that Criterion 3 of Article 71 of Directive 2001/83/EC and the European Commission Guideline "Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side effects of which require further investigation" does not apply.

Criterion 4: Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection).

This criterion is not applicable to Fortacin since the product is not to be administered parentally (for injection).

Other considerations:

Fortacin is included in a spray container. There are two containers authorised, one of 5 ml and one of 6.5 ml, which deliver 12 or 20 doses respectively (only the container of 5 ml is currently commercialised). One dose is equal to 3 actuations. The maximum daily dose is 3 doses with at least 4 hours between doses. The product information advises patients to discontinue use and seek medical advice if the product used as directed does not provide relief. CHMP considers that appropriate instructions and precaution for use are included in the product information for patients and that the spray containers are adequate for use without medical prescription.

9. Risk management plan

Safety concerns

All safety concerns have been removed following an update to align to GVP V rev2.

9.1. Overall conclusion on the RMP

☒ The changes to the RMP version 4.0 are acceptable.

10. Changes to the Product Information

As a result of this variation, sections 4.4, 4.8, 4.9 of the SmPC are being updated to reflect the change of legal status. The Package Leaflet (PL) and labelling are updated accordingly.

Changes are also made to the product information to bring it in line with the current QRD template version 10.1.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

[13] Butcher MJ, Zubert T, Christiansen K, Carranza A, Pawlicki P, Seibel S. Topical Agents for Premature Ejaculation: A Review. Sex Med Rev. 2019 Apr 12. pii: S2050-0521(19)30020-4. doi: 10.1016/j.sxmr.2019.03.003. [Epub ahead of print]

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

10.1.1. Quick Response (QR) code

The review of the QR code request submitted by the MAH is presented in a separate attachment to this report.

10.1.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.