CBG MEB

Public Assessment Report

Scientific discussion

Alprostadil Recordati 2 mg/g and 3 mg/g, cream

(Alprostadil)

NL/H/3303/001-002/DC

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This module reflects the scientific discussion for the approval of Alprostadil Recordati 2 mg/g and 3 mg/g, cream. The procedure was finalised on 6 August 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ASMF	Active Substance Master File
AUC	Area Under the Curve
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
DDAIP	Dodecyl-2-N,N-dimethylaminopropionate
ED	Erectile Dysfunction
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EF	Erectile Function
ERA	Environmental Risk Assessment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCl	Hydrochloride
ICH	International Conference of Harmonisation
IIEF	International Index of Erectile Function
IRB	Institutional Review Board
LADA	Lauric Acid Diethanolamine
LOGkow	Logarithm of octanol/water partition coefficient
LOQ	Limit of Quantification
LS	Least Square
MCID	Minimal Clinically Important Difference
MEB	Medicines Evaluation Board in the Netherlands
MAH	Marketing Authorisation Holder
$PEC_{surfacewater}$	Predicted Environmental Concentration in surface water
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SEP	Sexual Encounter Profile
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom
US	United States

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Alprostadil Recordati 2 mg/g and 3 mg/g, cream from Recordati Ireland Ltd.

The product is indicated for the treatment of men ≥ 18 years of age with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

A comprehensive description of the indications and posology is given in the SmPC.

Alprostadil Recordati contains alprostadil and the excipient dodecyl-2-N,N-dimethylaminoproprionate (DDAIP).Alprostadil is chemically identical to prostaglandin E1, the actions of which include vasodilatation of blood vessels in the erectile tissues of the corpora cavernosa and increase in cavernosal artery blood flow, causing penile rigidity. DDAIP is added to the formulation in order to optimize the absorption of alprostadil.
After application of Alprostadil Recordati the onset of erection is within 5 to 30 minutes. Alprostadil has a short halflife in man and improvement of erections may last from 1 to 2 hours after dosing.

This application is submitted in accordance with Article 8(3) application, (i.e. dossier with administrative, quality, pre-clinical and clinical data) with a known active substance.

The concerned member states (CMS) involved in this procedure were Cyprus, Czech Republic, Greece, Spain, Ireland, Poland, Portugal, Romania and Slovak Republic.

This cream was refused in the US (2008) and registered in Canada since 2010. The main reason for refusal in the US was the potential carcinogenicity of the excipient DDAIP at that time.

The non-clinical dossier is based upon the known safety of alprostadil and brings together the preclinical studies performed for three investigational programs for three separate products containing the novel excipient, DDAIP and DDAIP HCl as well as alprostadil. The studies employ the alprostadil topical cream for Alprostadil Recordati creams, both of which contain the novel excipient, DDAIP HCl and the drug alprostadil, and a third set of studies for Terbinafine HCl Nail Lacquer, which also contains the excipient, DDAIP HCl.

The clinical documentation comprises 9 phase 1 studies, 4 phase 2 dose-finding studies, 2 phase 3 studies and an extension study. Additionally 15 studies performed in China, some with a comparable but not the same formulation and others containing varying levels of DDAIP, were included. Some of the studies do not contain the uptake enhancer DDAIP, consequently the doses to be administered are higher (up to 1000 µg).

Scientific advice was given by the Dutch MEB and British MHRA in 2005, and by the German authority BfArM in 2007.

Although this application falls within the scope of Article 7 of the paediatric regulation no studies in children are submitted as the EMA has granted a class waiver for products intended for the treatment of erectile dysfunction.

II. QUALITY ASPECTS

II.1 Introduction

Alprostadil Recordati 2 mg/g and 3 mg/g are white to off-white creams. Each single use container contains 200 µg of alprostadil in 100 mg of cream (2 mg/g) or 300 µg of alprostadil (3 mg/g).

Alprostadil Recordati is supplied in Accudose, a single dose container. Accudose is a container consisting of a plunger, barrel, and protective cap provided in a protective sachet.

The excipients are: purified water, ethanol (anhydrous), ethyl laurate, hydroxypropyl guar gum, dodecyl-2-N,N-dimethylaminopropionate hydrochloride (DDAIP HCl), potassium dihydrogen phosphate, sodium hydroxide (for pH adjustment), phosphoric acid (for pH adjustment).

II.2 Drug Substance

The active substance is alprostadil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is the active isomer and is a naturally occurring form of prostaglandin E1. It is freely soluble in alcohol, soluble in acetone, slightly soluble in ethyl acetate, very slightly soluble in chloroform and in ether, and practically insoluble in water. Polymorphism is not known. It is unstable in aqueous solutions at pH <4 or >8 and undergoes dehydration. As the drug substance is dissolved in ethanol during the manufacturing process of the drug product, its initial physical form and particle size distribution are not relevant.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The synthesis comprises twelve synthetic steps. The starting materials are acceptable and controlled adequately. No Class I organic solvents are used. The active substance had been suitably characterized. It has been adequately demonstrated that the active substance is being used in many EU approved drug products for over many years, a discussion on genotoxic impurities may be omitted in line with the Q and A on this issue from the EMA.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for residual solvents, residual catalysts, and one specific related substance. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 4 years (stored at 5°C) and 12 months (stored at 25°C / 60%RH). Based on the data submitted, a retest period could be granted of 3 years when stored between 2°C and 8°C.

II.3 Medicinal Product

Pharmaceutical development
This alprostadil cream formulation was developed as a more convenient topical dosage form, and an alternative to the approved and former invasive treatments like Muse intrapenile stick and alprostadil injection. The development of the product has been described, the choice of excipients and their functions explained. The cream contains the excipient dodecyl-2-N,N-dimethylaminoproprionate HCl (DDAIP HCl) which was new for DCP procedures NL/H/2379 and 2080/001-002/DC. DDAIP HCl is a surfactant that should promote the absorption of alprostadil after penile application (in the urethra). The main development studies concerned the performance of DDAIP HCl, the applied stability overage of 10%, and the dispenser. The applied concentration range of DDAIP HCl was based on *in-vitro* permeation studies with alprostadil and *in-vivo* clinical studies. The proposed permeation enhancement characteristics of DDAIP HCl over the proposed range DDAIP HCl are supported by the clinical and non-clinical assessment. The stability overage for the active substance is acceptable in view of the observed degradation in the stability studies and the concentrations in the clinical batches. The single-use product is formulated and manufactured to have a low bioburden content, but it is not manufactured as a sterile product and does not contain preservatives. It has been demonstrated that a

preservative is not needed due to the preservative activity of the drug product itself. The stability results demonstrate adequate microbial quality over the whole shelf-life. A clear overview of the formulations and batches used in the clinical studies has been provided. The phase 3 clinical studies have been performed with the commercial formulation manufactured according the proposed process, although at a development site, not the commercial site. However, the submitted results of batch analysis and validation of the commercial batches manufactured at the proposed site confirm consistent quality of the drug product. The DDAIP HCl used for the clinical batches is from a different manufacturer than the proposed commercial manufacturer. This has been adequately discussed and substantiated by characterisation data and analytical results. The proposed dispenser has been used in the clinical studies and the stability batches. Accuracy of the dispenser is adequately controlled by batch-to-batch control of weight variation of the delivered dose, as % of target dispense weight, content uniformity and assay alprostadil.

Manufacturing process

In view of the manufacturing process, i.e. suspension in aqueous phase of oil-in-water emulsion, the low concentration and unit-dose, the instability of the active substance (low temperature, nitrogen purging, light protection), and the required low microbial burden, the process is a non-standard process in line with the Guideline on process validation. Appropriate, large scale validation data of eight batches have been provided of the process performed at the development manufacture site together with validation data of commercial-scale batches manufactured at the proposed site. The validation is appropriate.

Control of excipients

In-house specifications are applied for ethyl laurate hydroxypropyl guar gum and DDAIP HCl. Full information has been provided on novel excipient DDAIP HCl. The synthesis comprises three synthetic steps and recrystallisation. The starting materials are acceptable. Potential genotoxic impurities have been adequately discussed. Adequate characterisation of DDAIP HCl has been provided. The control specifications are suitable. A re-test of 24 months has been justified based on 18 months long term and 6 months accelerated stability data. An adequate specification is applied for hydroxypropyl guar gum. For the other excipients reference is made to the Ph. Eur.

Quality control of drug product

The product specification includes tests for appearance, identity, assay alprostadil and DDAIP HCl, degradation products of alprostadil and DDAIP HCl (1-dodecanol), pH, viscosity, oxygen content, leak test, microbial quality, uniformity of delivered mass as % of label claim, particle size distribution and uniformity of content. Wider shelf-life requirements are applied for assay alprostadil, DDAIP HCl, degradants, and pH. The methods are suitable and have been adequately validated.
Batch analytical data have been provided of all validation/stability batches. Results of batch analysis of commercial scale batches manufactured at the proposed site, and tested for all proposed specifications and with the proposed methods have been provided. Limits for known degradants are qualified in view of the stability results and as these are metabolites of endogenous PGE1 and present in comparable amounts in human ejaculate.

Stability of drug product

Stability data on the drug product have been provided of three batches of both strengths stored at long term (5°C) and accelerated conditions (25°C/60%RH). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging.
It is clear that the product in the proposed packaging is not very stable. The concentration of DDAIP HCl decreases due to sorption by the plastic packaging. Moreover, PGE1 degrades rapidly in the formulation. The justification of the safety of the levels of these degradation impurities is acceptable. These proposed specifications are also acceptable based on the statistical analysis of the stability results and the concentrations in the clinical studies.
The proposed combined shelf-life (9 month shelf-life for the 200 µg and an 18 month shelf-life for the 300 µg, with an allowance for room temperature excursion of 3 days for both strengths) is acceptable in view of the submitted stability data, but needs to be confirmed in stability studies. In view of the stability results with the product stored outside the sachet, the product should be stored in the sachet packaging. It is not clear whether this is solely due to light or also due to the absence of the nitrogen overhead in the sachet.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Alprostadil Recordati Crème has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The MEB has been informed that the first three commercial batches manufactured on the proposed site have demonstrated out-of-trend and out-of-specification results in the stability studies for appearance and assay. However, the root cause has been identified and actions are taken. Considering the corrective actions and the enhanced monitoring of the batches there is no objection to continuing production and releasing batches to the market.

The following post-approval commitments have been made during the procedure:
- The MAH committed to review the particle size specification when additional release and stability data, as well as safety data is generated
- The MAH committed that the temperature excursions studies will be repeated at end of shelf life on the next 2 batches of the 200 µg strength with application of the approved tests- and limits.
- The MAH committed to test for potential genotoxic impurities in DDAIP HCl in three commercial batches.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Good Laboratory Practice
With regard to GLP, the pivotal studies have been conducted in accordance with GLP regulations.
Some more exploratory studies have not. The latter is acceptable.

III.2 Pharmacology

Alprostadil Recordati contains alprostadil and DDAIP HCl. DDAIP is added to the formulation in order to optimize the absorption of alprostadil.
Safety pharmacology studies were only performed with DDAIP. No studies were submitted that evaluate the safety pharmacology of the combination alprostadil and DDAIP. No studies were submitted that evaluate the drug interaction between alprostadil and DDAIP. This is acceptable, as interactions are not expected.

III.3 Pharmacokinetics

The pharmaco- and toxicokinetic studies focused on the kinetics of DDAIP and its salt DDAIP HCl and not on the differences in kinetics of the innovative formulation alprostadil/DDAIP compared with the former formulation with active compound alone. Therefore, no conclusions can be drawn the influence of DDAIP on the pharmacokinetics of alprostadil.

Alprostadil
The metabolism of alprostadil occurs mainly in the skin after topical administration and after systemic exposure in the lung. Alprostadil is metabolized by oxidation and reduction steps into 13,14-dihydro-15-keto PGE1, 13,14-dihydro PGE1, and 15-keto-PGE1. The first two are biologically active but the last is inactive. In humans, alprostadil was mainly excreted as metabolites via the kidney.

DDAIP

The results of studies achieved in rats with the 14C-label, were used to determine the kinetics of DDAIP.

Due to large inter-individual variability and plasma levels below the limit of quantification (LOQ), interpretation of the DDAIP pharmacokinetics is difficult. The bioavailability of dual-radiolabeled DDAIP after dermal application on hair-free skin was ~5% in rat. No information was provided on the bioavailability in mouse and dog. The skin of the pre-clinical species, except (mini-) pig, are not representative for human skin and the penile skin is different than skin from other parts of the body with most likely higher bioavailability from penile skin compared to normal skin. Therefore, the estimated bioavailability of ~5% may is most likely an underestimation of the human bioavailability after topically administration on the penis.

DDAIP becomes systemically available in male dogs with AUC0-24h values ranging from <LOQ to 7.5 ng/mL*h after a single dose. After repeated dosing, systemic exposure of DDAIP increases to ~15-17 ng/mL*h suggesting some accumulation of DDAIP. In contrast, no signs of accumulation were present after repeated dosing in mice topically treated with DDAIP, but this is most likely due to the shorter half-life in mouse compared to dog. Half-lives of DDAIP ranged from ~6 hours in mice to ~60 hours in dogs. No information about volume of distribution and clearance in the pre-clinical species was available. In addition, dose-proportionality could not be assessed due to study limitations. Plasma protein binding of DDAIP is very high (>99%) in rat, dog and human plasma. The distribution of DDAIP in rats has only been determined after SC administration and not after dermal application on the penis. After SC administration, the highest tissue concentrations were in the kidney, bladder, skin, adrenals, stomach and gonads. Gender differences in distribution to tissues were only observed at the highest concentrations in males. After 72 hours, tissue radioactivity was still measurable indicating slow elimination from tissues.

DDAIP is rapidly metabolised to two (endogenous) compounds: N,N-dimethylalanine and 1-dodecanol. Additionally, in mouse, rat and dog plasma, a minor unstable metabolite is formed, DDAIP N-oxide. The metabolism of DDAIP to N,N-dimethylalanine and 1-dodecanol is via esterases in the skin, liver and plasma and not via CYPs. Carboxylesterase represents most likely the major biotransformation pathway. Furthermore, formation of the metabolite DDAIP N-oxide is catalyzed by FMO1. *In vitro*, degradation in human liver microsomes, skin homogenate or plasma is in general slower than in the pre-clinical species suggesting a longer half-life of DDAIP in humans than in the pre-clinical species. Dimethylalanine is the major component (90%) in rat and dog plasma.

DDAIP is most likely mainly excreted via urine, as N,N-dimethylalanine, in both rats and dogs. Excretion via faeces was a minor route of elimination.

Combination of alprostadil with DDAIP

Alprostadil may have an influence on plasma levels of DDAIP as differences in systemic exposure and maximum plasma concentrations were observed in male dogs when comparing the plasma levels of DDAIP when given in combination with alprostadil and without alprostadil. No pharmacokinetic studies were conducted after vaginal exposure to Alprostadil Recordati. This information is not considered to be crucial, as vaginal exposure is assumed to be less than penile exposure.

Both alprostadil and DDAIP become systemically available after dermal absorption. Currently, no clinical drug-drug interactions have been observed. As clinically both alprostadil and DDAIP exposures are very low to undetectable and both compounds are not metabolised via CYPs, no drug-drug interactions are expected via that pathway. Furthermore, interactions via esterases or plasma protein binding are also not expected based on the low systemic concentrations of both compounds.

III.4 Toxicology

Acute toxicity of alprostadil and DDAIP (HCl) was only tested after oral and intravenous administration, at very high doses in rats and mice. Since no significant systemic exposure is achieved in humans after topical administration of the cream, these studies are hardly relevant.

A multitude of studies has been performed to investigate the repeated dose toxicity of alprostadil cream formulation, DDAIP and DDAIP HCl, in male and female animals through various topical routes, subcutaneous and intravenous administration, in mice, rats, rabbits and dogs. Alprostadil is a known substance, and therefore the focus of the assessment has been on the new excipient DDAIP. The addition of DDAIP to alprostadil has only been investigated in female rabbits using the intravaginal route, where no significant effects were observed. The relevant species for this application, males, were not included in these studies.

The main point of concern with regard to toxicity of DDAIP is degeneration or atrophy of the seminiferous tubules of the testes, which was seen in the rabbit. These effects were seen in several rabbits after topical application of alprostadil including DDAIP or DDAIP alone, at a concentration of 5%. The effect appeared reversible. Sperm quality was not examined in this study. In a newly conducted rabbit study using Alprostadil Recordati cream containing 2.5% DDAIP, only a single rabbit was affected, and no effect on sperm count or morphology was evident in this study. Damage to the seminiferous tubules of the testes could have an effect on sperm generation and/or quality. A direct spermatoxic effect of DDAIP cannot be tested in vitro due to problems with solubility at physiological pH. The MAH should therefore perform a clinical post-authorization safety study in which the risk for sperm toxicity is examined. Further, this effect was included in section 5.3 of the SmPC and in the RMP.
Another finding of potential concern is thymic atrophy, seen in dogs treated topically for 28 days with alprostadil cream containing DDAIP. No atrophy was observed in the control groups, with or without DDAIP, and since a dose response was evident, it is likely that this effect is related to alprostadil. However, systemic exposure is negligible after topical use, and moreover, no such effect was seen in two other 28-day dog studies using the intrameatal route of administration. Further, no other signs of immunotoxicity were seen in any of the pre-clinical studies, or clinical trials, and therefore this finding is unlikely to be relevant for man.
Other findings after treatment with DDAIP were seen after subcutaneous administration. As DDAIP does not reach significant systemic exposure in humans when used in a cream, the effects seen in these animal studies are not relevant for humans.
Testing of mutagenic potential in bacterial cells was limited due to severe cytotoxicity. However, overall there is sufficient evidence to support the conclusion that neither alprostadil, DDAIP or DDAIP HCl have genotoxic potential.

Two carcinogenicity studies have been completed on DDAIP including a 26-week dermal application in Tg.AC mice and a 2-year subcutaneous dosing study in rats. Two other carcinogenicity studies were completed on DDAIP HCl including a dermal study in mice and a dermal study of terbinafine HCl Nail Lacquer (containing 0.5% DDAIP HCl) in rats. The transgenic mouse study, using a model specifically sensitive to dermally applied carcinogens, and used in this way several times for regulatory purposes, was unexpectedly positive, and DDAIP has been shown to induce papilloma's after dermal application. The other three studies were negative.
DDAIP has a similarity to cationic surfactant lauric acid diethanolamine (LADA), sharing with DDAIP the lauryl (C12) tail, and therefore its detergent action. Also LADA was tested in the TG.AC mouse and reported to be positive. Therefore the following points were discussed to come to a risk assessment for DDAIP:
1. Extensive use of LADA for more than 25 years in consumer products including those that are considered 'leave-on' products and expose mucous membranes support the safety and lack of tumorigenicity of this compound at concentrations up to 9%.
2. A survey of US approved drugs illustrated that a number of both prescription drugs and over the counter products tested positive in the Tg.AC transgenic mouse model.
Both LADA and DDAIP tested positive in the Tg.AC transgenic model. Papilloma formation in Tg.AC mice is positively correlated with irritation at the site of application. LADA and DDAIP are both detergents, and due to this characteristic this will probably lead to similar irritation. Overall, it can be concluded that the papilloma-inducing effect of DDAIP is caused by the irritation in this TG.AC mouse model, and is unlikely to be of human relevance.

No reproductive toxicity studies were performed with the salt form DDAIP HCl, nor were any studies done with a formulation also containing alprostadil. The MAH has provided information from which can be concluded that the presence of alprostadil in Alprostadil Recordati cream will not lead to significant higher exposure in women, than naturally occurring PGE1 in the ejaculate.

The reproductive toxicity studies in female animals are only relevant with regard to transfer of the cream including DDAIP from the male to the female. The MAH estimated that a maximum dose to which a female might be exposed, is 0.071 mg DDAIP. Apart from the fact that this dose is only estimated and no actual measurements were made, it can be assumed that the dose will be very low, and systemic exposure will be negligible. The MAH has not performed a study with the formulation intended for clinical use as is required according to the current guideline on local tolerance. Sufficient information has been gained from the repeated dose toxicology studies and clinical studies, therefore new local tolerance studies are not warranted.

Intrameatal administration in the dog caused epithelial hyperplasia when alprostadil cream containing DDAIP HCl (2.5%) was administered daily at a dose of 250 mg and intravaginal administration in the rabbit caused edema and erythema with a DDAIP HCl concentration of 1% and above. In mice when administered daily for 3 months on the skin, peeling and glazing of the skin and multifocal epidermal hyperplasia at the application site was observed at a 5% DDAIP HCl. Taken together these data suggest that daily administration of Alprostadil Recordati for extended periods could pose a risk of local irritation and subsequent regenerative response of the tissue.
No cytotoxicity was observed in the vaginal irritation potential *in vitro* study using human tissue for either DDAIP or DDAIP HCl.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The potential environment risk of Alprostadil Recordati was assessed according to the EMEA Guidance (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, Doc. Ref. EMEA/CHMP/SWP/4447/00). The assessment was conducted on the 200 µg/300 µg dose of alprostadil contained in Alprostadil Recordati.
The $\log_{Kow}$ value and the $PEC_{surfacewater}$ value of 200 and 300 µg alprostadil are 0.33 and 0.001 µg/L and 0.0015 µg/L respectively and below the action limits in the Phase 1 assessment. Alprostadil does not have any apparent risk for the environment at the 200 µg/300 µg dose contained in Alprostadil Recordati. Alprostadil Recordati can be considered to have minimum risk for the environment from the use, storage and disposal of the product following its prescribed usage in patients. As phase 1 assessment results were satisfactory, no further evaluation is required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Overview of studies
The application comprised 9 phase 1 studies, 4 phase 2, dose-finding studies, 2 phase 3 studies and the extension. During the clinical program 241 patients completed the phase 1 trials, 359 patients were enrolled in the Phase 2 dose finding trials and 1895 patients were enrolled in the Phase 3 trials for a total number of 2495 patients studied.

The most important phase 2 dose finding trials and the phase 3 trials are summarized in Table 1 and Table 2.

In these Phase 2 and 3 clinical studies where there were a total of 1605 patients treated with alprostadil cream at doses of 50, 100, 200, 300 µg alprostadil, which contained the novel excipient DDAIP or DDAIP HCl. In addition, there were 543 patients treated with the corresponding placebo cream formulation, which contained the novel excipient (DDAIP or DDAIP HCl).

Table 1 Clinical Development Program (Phase 2 dose-finding studies)

Study Number	Patients Enrolled/ Completed	Design	Purpose	Comments
MED 99-001	128 intended 29 randomized	Placebo controlled, randomized, double blind, multiple dose - at high dose levels 500, 1000, 1500 µg alprostadil	Develop preliminary efficacy and safety data on high dose cream	Study stopped by Sponsor due to higher than expected adverse effects
MED 99-002A	161 randomized 111 evaluable for efficacy	Placebo- controlled, double- blind, randomized, parallel, 6-week home use study in mild to moderate patients treated with 50, 100, 200 µg alprostadil	Develop preliminary efficacy and safety data at low doses	Useful data on mild to moderate patients. No 300 µg alprostadil group

MED 2000-002A	142 enrolled ITT 127 completed ITT-E 104 fully evaluated	Placebo- controlled, Double-blind, randomized, parallel, 6-week at home use trial in severe patients. 100, 200, 300 µg alprostadil studied	Develop preliminary safety and efficacy data on severe patients	Demonstrated efficacy and tolerability in severe patients and first use of the exact dose levels later used in Phase 3
MED 2000-007	27 randomized 26 evaluable	Instrumental measurement of erections in clinic setting, randomized, placebo, 4-way, crossover doses of 100, 200, 300 µg alprostadil	Complement clinical efficacy measures with instrumental in-clinic measurements	Few differences in efficacy between groups. Demonstrated tolerability to study medication

Table 2 Clinical Development Program (Phase 3 studies)

Study Number	Patients Enrolled/Completed	Design	Purpose	Comments
MED 2000-004	878 enrolled ITT 850 evaluable efficacy population ITT-E	3-month home use randomized, placebo-controlled, double- blind, parallel safety and efficacy study doses of 100, 200, 300 µg alprostadil Initial in-clinic safety check	Pivotal safety and efficacy	Demonstration of efficacy and safety on 100, 200, 300 µg
MED 2000-005	854 enrolled ITT 819 evaluable ITT-E	3-month, home use randomized, placebo controlled, double blind, parallel safety and efficacy study doses of 100, 200, 300 µg alprostadil Initial in-clinic safety check	Pivotal safety and efficacy	Essentially identical to MED 2000-004 . Demonstration of efficacy and safety on 100, 200, 300 µg
MED 2000-006	1161 treated for various lengths of time. 998 rolled over from the other Phase 3 studies. 163 new patients	Open-label safety and efficacy study; 12-month intended duration. Most patients rolled over from other Phase 3 studies doses of 100, 200 and 300 µg alprostadil	Primarily generate long-term safety and efficacy information	Interrupted by the Sponsor after about 6 months. Provides efficacy and primarily long-term safety data

The extension study (MED 2000-006) was initially planned for 12 months, but prematurely stopped after 6 months. The study was terminated early because it was halted by the Food and Drug Administration of the United States (FDA), based on concerns regarding the results of the Tg.AC mouse carcinogenicity study. This so-called 'clinical hold' on study MED 2000-006 was later lifted by the FDA.

Quality of clinical studies, compliance with GCP

All of the studies in the Alprostadil cream clinical program were conducted in accordance with Good Clinical Practices (GCP) IC requirements and approved by Institutional Review Boards (IRBs).

IV.2 Pharmacokinetics

Only low or no systemic plasma concentrations could be detected after application of a single dose of 100, 200 or 300 µg alprostadil. Low plasma concentrations of the almost inactive metabolite PGE0 are observed. These levels were above endogenous plasma levels. Peak plasma concentrations of the

15-keto-PGE0 metabolite are reached with 1h. AUC increased with increasing dose, however no clear dose proportional pharmacokinetics are observed.
Also low or now plasma levels of the excipient DDAIP are observed after application of single doses of 100, 200 and 300 µg.
PGE1 is following the known elimination pathway, i.e. most of it is metabolized in the lungs by dehydrogenase. DDAIP is eliminated by carboxylesterases in plasma. The systemic half-life of alprostadil in man has been shown to be short and varying between 30 seconds to 10 minutes in various tissues.
Considering the low or none detectable plasma levels of PGE1, its metabolites and DDAIP, the rapid elimination, no significant impact on the pharmacokinetics is expected in case of renal or hepatic impairment or in the elderly. In addition, patients with pulmonary disease may have a reduced capacity to clear the drug. In patients with adult respiratory distress syndrome, pulmonary extraction of intravascularly administered PGE1 was reduced by approximately 15% compared to a control group of patients with normal respiratory function.
Considering that Alprostadil Recordati will not be used in very critically ill patients, no concern is identified regarding special patient groups. The SmPC states conservatively that in case of use in pulmonary and renal impairment, the dose may need to be lowered in these populations due to impaired metabolism, which is agreed.

No interaction studies have been submitted. As alprostadil and DDAIP are very rapidly metabolised by esterases, drug-drug interactions are considered to have a little impact. Considering the very low plasma concentrations, drug interactions at the level of CYP enzymes are considered not a concern.

IV.3 Pharmacodynamics

No formal pharmacodynamic studies were submitted.

IV.4 Clinical efficacy

Phase II studies
Four dose response studies (MED 99-001, MED 99-002A, MED 2000-002A and MED 2000-007) were performed. The dose range studied varied from 100 to 1500 µg. Efficacy information from study MED 200-007 is lacking due to technical problems with the RigiScan device in that study. In these studies a total of 458 patients suffering from mild to severe erectile dysfunction (ED) were included. Of them 110 received placebo, 42 got 50 µg, 103 received 100 µg, 102 - 200 µg, 62 – 300 µg, 32 – 500 µg, 32 patients 1000 µg, and 32 got 1500 µg. Various efficacy endpoints were used among others IIEF, SEP rating scales and cardiovascular measurements (heart rate and blood pressure). Study MED 99-001, the study of the highest dose range 500-1500 µg, was terminated prematurely due to adverse events.
The doses varying from placebo to 300 µg showed a clear dose response relation. This choice is substantiated by the submitted dose-finding data. The changes in the IIEF score in the various studies combined were +0.5 after placebo, +4.1 after 100 µg, +5.5 after 200 µg and +9.44 after 300 µg. The MAH chose the 100, 200 and 300 µg dose for further evaluation in the phase III studies.

One of the phase I studies, study NEXSCIN 2001-001, evaluated the fate of the applied alprostadil after application. The scintigraphy evaluations of these patients revealed that following self administration by both correct and incorrect methods 98% of the administered dose of Alprostadil Recordati cream was retained in the fossa navicularis of the penis. Only one of the six subjects demonstrated some migration of the cream into the ureter.

Phase III studies
Studies MED 2000-004 and MED 2000-005 provide the main body of efficacy data. Both studies used the same protocol and will be discussed together. These two studies enrolled 1732 patients with mild to severe ED. Although standard inclusion criteria were used, exclusion criteria did not exclude patients with stable cardiovascular disease or patients non-responding to Viagra. Besides these populations the patient population included patients that suffered from diabetics, patients with hypertension, prostatectomy patients, and patients on other medications.

Demographic data indicate that the patient population is comparable with the populations reported in literature for this indication and those used to study the various PDE5 inhibitors.

Patients were treated with placebo, 100 µg, 200 µg or 300 µg alprostadil. Patients are evenly distributed over the various treatment groups.

The primary efficacy endpoints were responses to Questions 3 and 4 (vaginal penetration and maintenance of erection to ejaculation) of the SEP questionnaire and the erectile function (EF) domain of the IIEF. These endpoints are commonly used in ED in literature as well as in the assessment of efficacy for other products indicated for the treatment of ED for example PDE inhibitors.

The SEP is a validated six-item questionnaire. The first four questions concern the following: 1) attempts at vaginal intercourse; 2) patient's ability to achieve at least some erection; 3) ability to achieve vaginal penetration, and 4) maintenance of erection to ejaculation. The last two questions, 5) satisfaction with hardness of erection and 6) overall satisfaction with the sexual experience, are related to satisfaction.

In the pivotal studies the mean change in IIEF EF domain score was greater for the alprostadil treatment groups (ranging from 1.7 in the 100 µg alprostadil treatment group to 2.5 in the 200 µg alprostadil treatment group and 3.1 in the 300 µg alprostadil treatment group) when compared with placebo (–0.7) during the on-therapy period (all $p < 0.001$). Nevertheless, the absolute size of the favourable changes induced by treatment with alprostadil was modest. The 2.5 and 3.1 point improvement represents a statistically significant improvement over that group's baseline, however, with a score of 16.1 and 16.7 at the final visit; the average patient would still easily qualify for erectile dysfunction (normal score is >25). Further an increase of at least 4 point is generally considered as being clinical relevant.

Table 3 IIEF Erectile Function Domain Score – Endpoint Analysis (Intent-To-Treat Efficacy Population)

	Placebo	**Alprostadil (100 µg)**	**Alprostadil (200 µg)**	**Alprostadil (300 µg)**
Endpoint N[a]	408	421	405	417
Baseline Mean	14.0	13.6	13.6	13.6
Endpoint Mean[b]	13.3	15.3	16.1	16.1
Mean Change	-0.7	1.6	2.5	2.5
LS Mean Change	-0.7	1.6	2.5	2.4
SE of LS Mean Change	0.34	0.34	0.34	0.34
Median of Mean Change	0.0	1.0	2.0	2.0
Min to Max of Mean Change[c]	-22 to 21	-22 to 23	-19 to 24	-19 to 24
p-value[d]		<0.001	<0.001	<0.001

Note: The EF domain score is the sum of scores for Q1, 2, 3, 4, 5, and 15 in the IIEF. A higher score indicates a more favourable response.
a. If no post-baseline individual scores were available, baseline individual scores were not carried forward to replace the post-baseline missing scores. Therefore, the Endpoint N may be less than the Baseline N.
b. The endpoint analysis includes the last expected assessment as presented in the protocol (Visit 6) for completers or the last available assessment on treatment before the patient drops out or is lost to follow-up.
c. The wide ranges in the min and max values were indicative of the data listings.
d. Least square (LS) mean difference relative to placebo, from ANCOVA.
IIEF = International Index of Erectile Function; Max = maximum; Min = minimum; SE = standard error

For penetration success (SEP question 3), all results are statistically significant. In the 300 µg alprostadil group a mean improvement of 7.6 points is reported, which is a 15% improvement over baseline (see table 4). For PDE inhibitors (i.e. Viagra) the improvement for this score was about 90%. Even taking into account a 10% decrease in the placebo group, the improvement seen after use of Alprostadil Recordati is considered to be rather modest.

Table 4 Mean Percent (%) Vaginal Penetration Success (Intent-To-Treat Efficacy Population With At Least One Attempted Sexual Encounter)

	Placebo	**Alprostadil (100 µg)**	**Alprostadil (200 µg)**	**Alprostadil (300 µg)**
N	411	418	410	410
Baseline Mean (%)	55.9	53.4	52.9	49.9
Post-Baseline Mean (%)	51.2	56.6	58.2	57.5
Mean change (%)	-4.7	3.1	5.3	7.6
LS Mean Change (%)	-4.5	2.9	5.1	7.2
p-value[d]		<0.001	<0.001	<0.001

Note: Mean percent vaginal penetration success, measured as: (sum of all 'Yes' responses for Q3)/(sum of all 'Yes' responses for Q1)*100. Based on diary response on Sexual Encounter Profile: Question #1: Did you attempt to have a sexual encounter? and Question #3: Were you able to insert your penis into the partner's vagina?.
a. Least square (LS) mean difference relative to placebo, from ANCOVA.

The mean change for ejaculation success (SEP question 4) was lower in the placebo group than in the alprostadil treatment groups (see table 5). Again the extent of improvement produced by treatment with Alprostadil Recordati is moderate. After PDE treatment (*i.e.* Viagra) the increase in the active treated group is about 100% where in the Alprostadil Recordati treated group the increase is a modest 55% at best.

Table 5 Mean (%) Percent Ejaculation Success (Intent-To-Treat Efficacy Population With At Least One Attempted Sexual Encounter)

	Placebo	**Alprostadil (100 µg)**	**Alprostadil (200 µg)**	**Alprostadil (300 µg)**
N	410	418	410	410
Baseline Mean (%)	29.4	31.3	27.6	28.7
Post-Baseline Mean (%)	30.3	38.9	41.9	38.5
Mean change (%)	0.8	7.6	14.3	9.8
LS Mean Change (%)	0.4	7.0	13.8	9.1
p-value[a]		0.003	<0.001	<0.001

Note: Mean percent ejaculation success, measured as: (sum of all 'Yes' responses for Q4)/(sum of all 'Yes' responses for Q1)*100. Based on diary response on Sexual Encounter Profile: Question #1: Did you attempt to have a sexual encounter? and Question #4: Did your erection last long enough for you to complete intercourse with ejaculation?
a. Least square (LS) mean difference relative to placebo, from ANCOVA.

For the primary efficacy endpoints the pivotal studies show a statistically significant superiority over placebo, but the clinical relevance of the found effect remains modest. The results from the IIEF show a clinically insignificant effect of 3.1 for the highest treatment group, whereas an increase of at least 4 points is considered clinically relevant. The results obtained with SEP #3 and #4 appear to be less compared to PDE inhibitors.

The secondary endpoints (remaining questions of the IIEF and SEP score, Global Assessment Questionnaire and Patient Self Assessment of Erection) support the observations made for the three primary endpoints.

As a response to efficacy concerns raised during after the initial registration round, the MAH performed a responder analysis. According to the publication of Rosen *et al.* [1] the minimal clinically important difference (MCID) for the EF domain was 4, with estimated sensitivity and specificity of 0.74 and 0.73, respectively. Araujo et al. reported that the MCID for SEP Q2 was 21.4%, with estimated sensitivity of 0.55 and specificity of 0.73; the MCID for SEP Q3 was 23.0%, with estimated sensitivity of 0.72 and specificity of 0.78[2]. This information is used to perform a responder analysis.

Responder analyses of the total population (MED 2000-004/005) indicated that close to 40% of patients achieved a clinically significant improvement of their IIEF-EF score when treated with either the 200 µg or 300 µg dose. The ability to penetrate the vagina (SEP-2) with alprostadil cream is most consistent with the 300 µg dose (about 36% reported a clinical relevant improvement), achieving statistical significance within all disease severity levels relative to placebo; whereas the 200 µg dose level demonstrated statistically significant efficacy in both the moderate and severe disease categories (clinical relevant effect in 33% and 26% of the patients). The maintenance of the erection resulting in ejaculation was assessed in SEP-3. All three dose levels allow maintenance of the erection to achieve an ejaculation, especially in the moderate to severe ED patients (clinical relevant effect were reported in 25% of the patients using the 200 µg dose and 31% of the patients after administration of the 300 µg dose). Considering the ability to achieve the normal IIEF-EF level, i.e. ≥26, the 100 µg dose is efficacious in mildly affected patients (clinical relevant response in 11%), the 200 µg dose gives mild to moderate patients the ability to attain normal IIEF-EF levels (clinical relevant response in 20%). The

[1] Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol. 2011 Nov;60(5):1010-6
[2] 2 Araujo AB, Allen KR, Ni X, Rosen RC. Minimal clinically important differences in the vaginal insertion and successful intercourse items of the sexual encounter profile. J Sex Med. 2012 Jan;9(1):169-79

300 µg dose reaches statistical significant efficacy in all levels of ED severity (clinical relevant response in 17%).
Similar results to those of all patients were generally observed within the subpopulations (Viagra, failures, diabetic, cardiac, post-prostatectomy and hypertensive patients, < 65 years of age and > 65 years).
Alprostadil treatment in these subpopulation groups resulted in a substantial improvement in the ability of the patient to insert their penis into their partners' vagina (SEP question 3) and to have successful intercourse to ejaculation (SEP question 4) compared to placebo. In general the 200 or 300 µg alprostadil doses were more effective compared to placebo and to the 100 µg dose in all patient subpopulation groups.
In general, there was a statistically significant dose response overall improvement of erections with all doses of alprostadil compared to placebo in all of the patient subpopulation groups, except with the 100 µg dose in the Viagra failure patient subpopulation.

Over the 12 weeks the results remain stable in the pivotal studies. For the MED 2000-006 study, the primary reason for discontinuation was the sponsor's decision to terminate the study ahead of schedule when it was halted by the FDA.

Of the entire group of 1161 subjects treated with any alprostadil dose, less than 5% discontinued because of an adverse event. Alprostadil cream at all tested doses was effective in improving and sustaining erections. This was particularly evident in subjects who remained in the study until Study Closure. The long term safety and efficacy of alprostadil cream was addressed in MED 2000-006 study. At the end of the 3 months trial about 50% of subjects in any of the active treated patients had a clinically relevant IIEF-EF score change of > 4 compared with placebo (24%). Following the switch to 200 µg for a month and 300 µg for another 5 months 79% of subjects had an IIEF-EF score change > 4. The SEP-2 and SEP-3 change from baseline was 36.7% and 40.9%, respectively. This shows that for the patients continuing treatment the efficacy was preserved. Further the responder analysis indicates that 40% of the patients experience a clinical relevant effect; the high withdrawal rate due to ineffectiveness is therefore not unexpected.
Compared with available data from PDE inhibitors the effects seen with alprostadil are moderate at best. An indirect comparison with the data from the Muse dossier (alprostadil urethral stick, UK/H/0272/001-004/MR) is not possible, as the clinical endpoints do not match.

Fifteen studies were performed in China most with a comparable but not the same formulation. Some of the alprostadil formulations studied did not contain the uptake enhancer DDAIP, consequently the doses to be administered are higher (up to 1000 µg), while other studies evaluated various levels of DDAIP. Given the lack of equivalence between the formulation applied and the Chinese formulation, and because the Chinese formulation is administered at higher doses (up to 1000 µg) than the formulation applied for (200 or 300 µg) and there are some differences in the formulation excipients, results obtained in the Chinese studies cannot be extrapolated. Results are therefore not reported.

IV.5 Clinical safety

The safety data submitted by the MAH consists of phase 1, 2, and 3 studies with at total of 3308 exposed male patients, of which 2049 have been administered at least one active dose of alprostadil. In addition the MAH performed 6 phase 1 skin irritation studies which did not show evidence of significant local toxicity of DDAIP (HCl) and/or alprostadil, although the site of application was mainly on the forearm and paraspinal region which cannot be extrapolated to the glans penis. Additionally, clinical evaluation demonstrated that DDAIP had no potential for sensitisation or phototoxicity.

In the 2 pivotal phase 3 trials, 1732 patients were treated, of which 434 received placebo and 1298 received active treatment in doses of 100, 200 and 300 µg alprostadil. Patients were treated for a duration of 12 weeks with a mean of 17-18 applications per patient. Subsequently a phase 3 open-label extensions study was performed which yielded data on 300 patients exposed for more than 6 months, and 148 patients exposed for up to 9 months. From these 300 patients 120 ad exposure for which is not in line with ICH E1 and recommendations of the Scientific Advice. However, safety data for 6 months instead of 12 months could be acceptable based upon the fact that alprostadil is a known active substance with an established safety profile. Furthermore, considering the intermittent nature of dosing and its short half-life and duration of action, long-term safety issues of alprostadil are not likely to occur. The long-term safety of DDAIP HCl are limited. The MAH has added long-term safety to the

Risk Management Plan (RMP). As Alprostadil Recordati is not marketed, post-marketing data is currently not available.

In the studies, a wide range of patients were investigated (aged 21-87); the population included patients which were considered difficult to treat (diabetic, cardiac, prostatectomy or hypertensive patients and patients who have failed previous therapy with Viagra). This can be considered representative for the population of intended use.
Overall, the safety data submitted is considered sufficient in terms of number of patients, number of applications and duration of exposure.
In the phase 2 and phase 3 studies, patients who were considered intolerant as determined by an in-clinic test dose, were excluded from further treatment. This is different from the population of intended use as such precaution is not deemed necessary by the MAH for the market situation. Considering the small number of excluded intolerants in the pivotal phase 3 studies (0.4%), this is acceptable.

The adverse event (AE) profile derived from the pivotal phase 3 studies (MED 2000-004 and MED 2000-005) showed a dose effect and is heavily dominated by transient local urogenital reactions at or near the application site. These were reported by 13.1% in the placebo group, 36.2% in the 100 µg, 41.9% in the 200 µg, 42.9% in the 300 µg alprostadil group. Most commonly reported urogenital reactions were penile burning, genital pain and penile erythema (respectively 21.7%, 14.7%, 9.5% for the alprostadil treated groups). The majority of these AEs were mild to moderate in intensity, considered treatment-related and transient in nature.
As expected for this type of drugs, systemic vasodilating symptoms were also reported, but the incidences were acceptable: dizziness, hypotension and syncope were reported at respectively 1.0%, 0.2% and 0.4% in the alprostadil treated groups.
The incidences of priapism and prolonged erection are low and acceptable (0.1% in MED 2000-004/MED 2000-005 and 0.4% in MED 2000-006). No serious penile events, such as penile fibrotic complications, were reported.
No events were reported in subjects that would indicate local carcinogenicity at the site of application.

In the 10 phase 1, 2 and 3 studies, a total of 6 serious adverse events (SAEs) reported by 4 patients were considered treatment-related: syncope (200 µg), hypotension and dizziness (200 µg), ECG abnormal (300 µg), sinus bradycardia and lab test abnormal (300 µg). Vasodilating symptoms can be expected of this type of drugs.

Concerning cardiovascular events specifically: In the pivotal phase 3 studies, no difference in cardiovascular events was identified between the placebo, 100 and 200 µg groups, but a higher number of events were reported for the 300 µg group. Serious ischaemic cardiac events were reported by 2 (0.5%), 0 (0%), 1 (0.2%) and 6 (1.4%) patients in the placebo, 100, 200 and 300 µg treatment groups, respectively. All patients had underlying cardiovascular disease and/or risk factors and the events were considered not product related. Although there is no clear indication that alprostadil increases the risk of cardiovascular events (other than the vasodilative effects), it cannot be excluded that patients with underlying disease/risk factors are at increased risk in combination with increased sexual/physical activity. The MAH has added use in patients with cardiovascular and cerebrovascular conditions to the RMP. Furthermore, SmPC statements have been strengthened in this regard.

Partner AEs were reported by 4.8% in the placebo group, 5.8% in the 100 µg, 9.5% in the 200 µg, and 7.6% in the 300 µg alprostadil group. Most commonly reported were local vaginal reactions, in particular vaginal burning and vaginitis. These AEs were mild and moderate in intensity, considered treatment-related and transient in nature. The partner AE profile is considered acceptable with no apparent safety issues.

The effects of Alprostadil Recordati on the oral or anal mucosa have not been studied. The MAH has appropriately revised the RMP and SmPC in this regard.

The rates of discontinuation due to AEs in the pivotal phase 3 studies were dose-dependent and higher for the 300 µg group as compared to the 200 µg group. The observed rates were 0.9%, 1.8%, 4.0% and 7.6% for the placebo, 100, 200, and 300 µg treatment groups, respectively. Of note is the much higher discontinuation rates due to AEs in the main phase 2 studies (MED 99-002A and MED 2000-002A) with the 200 and 300 µg treatment as compared to the phase 3 studies. The reason for this discrepancy is not clear.

By far the most common AEs resulting in discontinuations were local urogenital symptoms, in particular penile burning (1.2%) and genital pain (0.9%). Of the partners, 0.4% discontinued due to AEs. The most common AEs leading to partner discontinuations were vaginal reactions.

Analysis of laboratory parameters, ECG and physical examinations did not reveal meaningful effects of the study medication. No safety concerns were identified. Furthermore, there is no safety concern with regards to immunological events or with regards to drug interactions.

An evaluation of AEs was performed in patient sub-populations that were considered difficult to treat: diabetic, cardiac, prostatectomy or hypertensive patients and patients who have failed previous therapy with Viagra. Overall, the AE rates and pattern do not differ from the total safety population with the exception of some AEs related to the underlying disease being more frequently reported, which can be expected. There were no apparent differences between the AE rates of commonly reported events in patients <65 and ≥65 years of age.

In summary, the data of the pivotal phase 3 studies (MED 2000-004 and MED 2000-005) showed that the AE profile of Alprostadil Recordati is acceptable and in line with what can be expected for a topical formulation of alprostadil. The safety profile is dose-dependent. Although overall AE rates do not differ much between doses, the severity/seriousness of events appears to increase with increasing dose. In comparison to the 200 µg treatment, the 300 µg treatment had a less favourable safety profile with higher rates for severe AEs, serious AEs, discontinuations due to AEs and cardiovascular events.

Extension study MED 2000-006 confirmed the AE profile of Alprostadil Recordati when used for a longer period. The nature of the AEs in this study is similar to that of the pivotal phase 3 trials, but the AE rates were lower. Similarly to the pivotal phase 3 studies, most commonly reported were transient local urogenital symptoms.

In conclusion, the safety profile of Alprostadil Recordati appears acceptable in terms of rate, nature, severity and seriousness of reported AEs and laboratory findings. The AEs were line with what can be expected for a topical formulation of alprostadil and no unexpected clinical safety findings have been identified. It appears in general to be comparable with Muse and as expected of a topical formulation it has more local reactions, but appears to have less systemic reactions as compared to Viagra. The safety profile is dose-dependent, whereby the 300 µg treatment had a less favourable safety profile as compared to the 200 µg treatment.
The lack of data with regards to long-term safety and use in anal/oral sex, as well as the use in patients with cardio- and cerebrovascular conditions have been included in the RMP, with revisions of the SmPC with regard to the latter two issues.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Alprostadil Recordati.

Summary of the RMP

Important identified risks	- Spermatoxicity - Hypotension; Dizziness; Syncope - Priapism - Carcinogenicity
Important potential risks	- Embryotoxicity - Use in patients with cardiovascular or unstable cerebrovascular conditions - Possible interaction with: • PDE-5 inhibitors • Penile implants • Smooth muscle relaxants • Sympathomimetics, decongestants and appetite suppressants • Antihypertensives and vasodilators • Anticoagulants and platelet aggregation inhibitors

	- Urinary tract infection
Missing information	- Long term safety data for alprostadil - Patients with a history of: • Myocardial infarction • Neurological disease • Spinal injury • Pulmonary disease • Renal impairment • Hepatic impairment

For the risk spermatoxicity more information needs to be collected to further analyse root cause and identify a need for possible further risk minimisation measures. The MAH has committed to conduct a post-authorization clinical study to assess the effect of repeated Alprostadil Recordati (300 µg) administration on semen parameters over a twenty-six week period. The proposed study design is a randomized, double-blind, placebo-controlled parallel group safety study.

Periodic Safety Update Report (PSUR)
The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. A Pharmacovigilance System Master File (PSMF) has been provided in accordance with the new legislation. No additional pharmacovigilance activity is currently warranted. Alprostadil is included on the EURD list for various indications. Products authorised for the treatment of erectile dysfunction have been assigned a five-year PSUR submission frequency. As Aprostadil Recordati had a new administration form and contains the excipient DDAIP, for which the experience is limited, a 6-monthly PSUR-cycle was followed. Five 6-monthly PSURs were provided. Currently PSURs for alprostadil are submitted for the single assessment procedure (PSUSA) according to the periodicity stipulated in the European Union Reference Date list.

IV.7 Discussion on the clinical aspects

Benefit/Risk assessment

Benefits
The pivotal studies including 1734 patients with ED demonstrate a consistent statistical significant effect over placebo viewed individually or combined. The magnitudes of the effects observed in primary efficacy variables demonstrate the statistical superiority of all three doses to placebo and furthermore show that the 200 µg and 300 µg alprostadil doses produce consistently larger results than the 100 µg alprostadil dose. Responder analysis shows a clinical relevant effect in about 40% of the patients treated with either 200 µg or 300 µg. Similar results to those of all patients were generally observed within the subpopulations (Viagra, failures, diabetic, cardiac, post-prostatectomy and hypertensive patients, < 65 years of age and > 65 years). Further the responder analysis demonstrates a better efficacy in special patient populations (*i.e.* PDE-5 inhibitors failure, patients excluded for PDE-5 treatment) for the 300 µg.

Uncertainties with regard to benefits
Although the absolute size of the favourable changes induced by treatment with alprostadil were modest, the responder analysis shows a clinically relevant response in about 40% of the patients treated.

Results obtained in a six months extension indicated that less than 5% discontinued because of an adverse event. Alprostadil cream at all tested doses was effective in improving and sustaining erections. This was particularly evident in subjects who remained in the study until Study Closure. The primary reason for discontinuation was the sponsor's decision to terminate the study ahead of schedule.

Risks
The clinical safety profile of alprostadil appears acceptable in terms of rate, nature, severity and seriousness of reported AEs and laboratory findings. No unexpected clinical safety findings have been identified. The AEs were in line with what can be expected for a topical formulation of alprostadil. The safety profile of alprostadil is dose-dependent. In comparison to the 200 µg treatment, the 300 µg treatment had a less favourable safety profile with higher rates for severe AEs, serious AEs, discontinuations due to AEs and cardiovascular events.

The AE profile was heavily dominated by transient local urogenital reactions at or near the application site. Most commonly reported urogenital reactions were penile burning, genital pain and penile erythema. Systemic vasodilating symptoms (dizziness, hypotension, syncope) and prolonged erections/priapism were reported at incidences comparable to those known for Muse. The related SAEs were syncope, hypotension, dizziness, ECG abnormal and sinus bradycardia. Cardiovascular events were reported in patients with underlying disease and/or risk factors. Hence, it cannot be excluded that patients with underlying disease/risk factors are at increased risk in combination with increased sexual/physical activity that is associated with alprostadil use. This has been added to the RMP. The proposed risk minimization and SmPC statements are considered acceptable.

Uncertainties with regard to risks

There is insufficient evidence to conclude that the effect of degeneration of seminiferous tubules in the testis of rabbits due to local treatment with DDAIP is not relevant for humans. A direct spermatotoxic effect could not be tested in vitro. Since one of the reasons men will use this product is to be able to produce offspring, it is important to know whether fertility might be affected. The MAH therefore committed to perform a clinical post-authorization safety study in which the sperm quality of users of Alprostadil Recordati is examined and the SmPC is adjusted accordingly.

Further to this, data on long-term safety is lacking. This is of particular concern for DDAIP HCl. Long-term safety is addressed in the RMP.
The effects of Alprostadil Recordati on the oral or anal mucosa has not been studied. The RMP and SmPC have been revised in this regard.

Benefit-risk balance

From a clinical point of view, the pivotal studies demonstrate a consistent statistical significant superiority over placebo. Further the clinical relevance is demonstrated for about 40% of the patients treated. Indirect comparison with the results published for PDE5 inhibitors indicate a much lower effect for the alprostadil cream, while comparison with other alprostadil containing products (Muse) is hampered by different endpoints and the lack of direct comparative trials. On this level no difference can be seen between the various alprostadil containing products (i.e. comparable number of patients withdrawn due to inefficacy and successful intercourse)[3]. The mode of application for Alprostadil Recordati, however, is considered superior.

A dose/response plateau is demonstrated for the alprostadil cream 200 and 300 µg in patients with mild to moderate ED. Further the dose/adverse event ratio showed a plateau between 200 and 300 µg. In severe patients, the 300 µg dose showed better efficacy to that of the 200 µg, while the safety profile of the 200 µg was comparable to the 300 µg dose in these group of patients with severe ED.

Clinically relevant effects were demonstrated in risk populations with medical history of cardiac disease, hypertension, diabetes and prostatectomy (currently all excluded from PDE-5 inhibitor treatment). In these populations the 300 µg appeared to be more efficacious compared to the 200 µg dose. For these special patient groups a starting dose of 300 µg is acceptable.

The results of the responder analysis show that 40% of the patients experience a clinically relevant effect. In the other alprostadil containing product (Muse) also a high percentage of patients withdrew due to inefficacy (over 30% after 3 months). For the patients continuing on treatment the efficacy is maintained over at least a period of 9 months.

In conclusion the benefit/risk ration of Alprostadil Recordati is positive.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
Men between the ages of 21 and 64 years were used as participants who may be potential users of the product. The testing was performed over 7 sessions and involved a total of 44 participants. A set

[3] Padma-Nathan H, Hellstrom WJG, Kaiser FE et al. Treatment of men with erectile dysfunction with transurethral alprostadil. The New England Journal of Medicine 1997336; No. 1(1-7).

of 13 questions was used to assess key safety information and the participants' ability to find and understand the information as well as the participants' comments regarding layout, language and impression of the PL as a whole.
In the first few rounds, several questions did not meet the endpoint criteria for finding and understanding the information. The PL was therefore revised and additional interview sessions were conducted thus resulting in 7 sessions involving 4 different versions of the PL.
The 20 participants from Sessions 5, 6, and 7 (Groups 2 and 3) that were tested using the final version of the PL, demonstrated that the leaflet met the endpoint criteria for all questions except question number 2 and 4. For Group 2, question number 2, relating to partner side effects and question number 4, relating to potentially serious side effects met the criteria for locating the information in 90% of participants but did not meet the criteria for understanding the information. In the confirmatory group, Group 3 only question number 4 did not meet the criteria for understanding (80%) but did meet de criteria for locating the information.
Based on the test results the member states agree with the conclusions of the readability report. The results have shown that the information most relevant to the patient can be found in a good way. Even though not al questions met the criteria for understanding the information, the RMS is of the opinion that this information cannot be explained in the leaflet any clearer. The user testing as conducted by the MAH is therefore acceptable

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The member states, on the basis of the data submitted, considered that Alprostadil Recordati 2 mg/g and 3 mg/g, cream demonstrated a satisfactory risk/benefit profile in the indication *treatment of men ≥ 18 years of age with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.*
The product has a proven chemical-pharmaceutical quality. The non-clinical data in support of the application is sufficient and covers data on both the excipient DDAIP and alprostadil.

From a clinical point of view, the pivotal studies demonstrate a consistent statistical significant superiority over placebo. Further the clinical relevance is demonstrated for about 40% of the patients treated. Indirect comparison with the results published for PDE5 inhibitors indicate a much lower effect for the alprostadil cream.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The member states, on the basis of the data submitted, considered that adequate evidence of efficacy and safety has been demonstrated for the approved indication and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 August 2015.

Post-approval commitments have been made during the procedure:
- Commitments relating to the quality of Alprostadil Recordati are listed on page 6 of this report.
- Pharmacovigilance: the MAH committed to perform a PASS to study the risk for sperma-toxicity.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval / non approval	Assessment report attached
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Replacement or addition of a site where batch control/testing takes place. Replacement or addition of a manufacturer responsible for importation and/or batch release.	NL/H/3303/IA/002/G	IA/G	14-10-2015	10-11-2015	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products Addition of a manufacturing site for which carries out all manufacturing operations for the finished product, primary packaging, secondary packaging and batch control testing. The manufacturing process and specifications remain unchanged.	NL/H/3303/IB/001/G	IB/G	21-10-2015	24-11-2015	Approval	N
Addition of a new specification parameters. Deletion of a non-significant specification parameter. Replacement or addition of a supplier Change in the specification parameter for thickness of the foil.	NL/H/3303/IB/003/G	IB/G	21-01-2016	20-02-2016	Approval	N
Change in the immediate packaging of the finished product	NL/H/3303/2/IB/004	IB	01-02-2016	24-02-2016	Approval	N
Change in SmPC, not already covered by the Classification Guideline, for which no new quality, pre-clinical, clinical or pharmacovigilance data are provided.	NL/H/3303/1-2/IB/005	IB	20-06-2017	24-07-2017	Approval	N
Addition or replacement of a specification parameter as a result of a safety or quality issue Deletion of a supplier	NL/H/3303//IB/006/G	IB/G	13-09-2017	10-10-2017	Approval	N