WITHDRAWAL ASSESSMENT REPORT
FOR
INTRINSA

International Nonproprietary Name:
TESTOSTERONE

Procedure No. EMEA/H/C/000634/II/0013

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Scientific discussion

Introduction

Intrinsa is a transdermal patch containing testosterone and it was approved (July 2006) for use in the following indication:

> "*Treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant estrogen therapy*".

This variation application concerns an extension of the indication for Intrinsa to include all menopausal women with Hypoactive sexual desire disorder (HSDD), i.e. a potential expansion of the use of the product to a considerably larger patient population. Since the approval, Intrinsa has only been launched in six European countries (France, Germany, Ireland, Italy, Spain and the UK) and the usage has generally been low.

Each transdermal patch of 28 cm^2 contains 8.4 mg testosterone and provides 300 micrograms of testosterone per 24 hours. The recommended daily dose of testosterone is 300 micrograms, which is achieved by applying a patch twice weekly on a continuous basis. The patch should be replaced with a fresh patch every 3 to 4 days. The application for this extended indication includes two pharmacokinetic studies, four new phase 3 efficacy and safety studies and one endometrial safety study.

Clinical aspects

Background

Female sexuality is a highly complex entity reflecting an interplay of many psychological, psychosocial and cultural factors. In a very simplified description, a woman's sexual arousal consists of mental excitement and physiological genital response, where both a number of psychological and biological factors govern arousability. The complexity of female sexuality is reflected in female sexual dysfunction, the aetiology of which appears multifactorial, the diagnosis is often imprecise and the true prevalence is poorly known. The most commonly reported sexual disorder is loss of desire, interest, pleasure, and global satisfaction (Laumann 1999; Hayes 2008; Moreira 2008).

HSDD has been defined by both the American Psychiatric Association and an international consensus conference. The consensus definitions and classifications were built on the existing framework of the International Classification of Diseases-10 and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association), which were previously limited to consideration of psychiatric disorders. The occurrence of decreased sexual desire, if it does not cause distress or difficulty, is not considered a condition requiring intervention.

HSDD may occur in both surgically menopausal (SM) and naturally menopausal (NM) women, with similar prevalence in the groups. The WISHeS survey, conducted among European women in four major EU countries, found that 42% of NM women and 46% of SM women reported low sexual desire (Dennerstein 2006).

Estimates of the proportion of women having low sexual desire has been reported to range from 7% to 33% in studies done in the US, Europe and Australia, depending on the population studied and the operational definition used (Bancroft 2003; Johnson 2004; Laumann 1999; Dunn 1998; Osborn 1988; Geiss 2003; Fugl-Meyer 1999; Najman 2003; Richters 2003).

The rationale for use of testosterone in treatment of HSDD in menopausal women is based upon the fact that serum testosterone concentrations in women decline abruptly after surgical menopause and steadily with age and have been shown to be similar and low in both SM and NM women. However, although hormones appear to play an important role in female sexual function, there is no clear correlation between endogenous hormone levels and female sexual function. Moreover, although testosterone plays a role in sexual functioning, no specific testosterone concentration has been

identified as a minimum level necessary for preservation of sexual desire in women (Bachmann 2002, Braunstein 2002).

For some menopausal women, the decrease in testosterone level may contribute to the development of HSDD. Testosterone circulates as free testosterone and testosterone bound to albumin or Sex Hormone Binding Globulin (SHBG). There is an inverse relationship between SHBG and free testosterone levels. SHBG concentrations are affected by various factors, including body mass, menopause, hyperthyroidism, cirrhosis, insulin and growth hormone levels, and some drugs such as glucocorticoids, some androgens, some antiseizure drugs, and oral oestrogen and progestogen.

In previous studies of Intrinsa, women on oral oestrogen had a large range of SHBG concentrations, compared with patients on transdermal oestrogen. In those studies, women on oral conjugated equine oestrogen (CEE) had high SHBG and low free testosterone and little or no clinical effect of Intrinsa on their HSDD.

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This variation application concerns an extension of the indication for Intrinsa to include all menopausal women with Hypoactive sexual desire disorder (HSDD), i.e. a potential expansion of the use of the product to a considerably larger patient population. Since the approval, Intrinsa has only been launched in six European countries (France, Germany, Ireland, Italy, Spain and the UK) and the usage has generally been low.

Non clinical aspects

The applicant did not submit any new non-clinical data to support this variation application to extend the current indication. Testosterone is an endogenous, well-known substance and the toxicity of testosterone in animals is well documented in the scientific literature. It is known that testosterone is not genotoxic, but testosterone produces tumours in a range of organs, including endometrium, mammary gland and liver, in rodents when administered at high doses. This profile is consistent with the hormonal pharmacology of the compound. Testosterone can have adverse effects on the developing foetus and should not be used by women who are, or who are likely to become, pregnant.

In conclusion, testosterone has a well-known pharmacological and toxicological profile and further non-clinical data are not deemed necessary for this variation application since the value of additional data for the assessment of effects in clinical long-term use would be limited.

Environmental Risk Assessment

An Environmental Risk Assessment was submitted by the MAH. The applicant argues that it is not expected that the application of Intrinsa for the treatment of hypoactive sexual desire disorder (HSDD) in all menopausal women would cause an increase of testosterone on the EU-market.

However, the applicant has also as a precaution conducted a literature review on the effects of testosterone on aquatic organisms and the literature review well covers potential environmental effects of testosterone. The literature contains studies on the toxicity of testosterone to invertebrates, fish, and algae.

Barbosa et al. (2008) studied the toxicity of testosterone in static acute and semi-static chronic exposures with *Daphnia magna*. In a two day acute toxicity test, there were no effects on survival or immobilization at concentrations up to 6,200 µg/L. During the 21 day reproduction test, both fecundity and fertility were affected at 310 µg/L but not at 150 µg/L testosterone. Mu and LeBlanc (2002) studied the effects of testosterone on *D. magna* in a static renewal, 21-day survival and reproduction test. During this test, approximately 1,440 µg/L of testosterone had no effect on offspring production or the percent of offspring containing abnormalities. Exposure of daphnids to approximately 1,730 µg/L testosterone appeared to cause a significant increase in abnormalities and a reduction in total offspring per female. Radix et al. (2002) exposed the rotifer, *Brachionus calyciflorus*, to testosterone in a chronic asexual reproduction test (three days). Testosterone at 2,560 µg/L had no effect on total number of females or the intrinsic rate of population increase ('r') while exposure to the next higher

concentration, 6,400 µg/L, was associated with reductions in these parameters. Preston et al. (2000) evaluated asexual reproduction and fertilization of females in *B. calyciflorus* exposed to 0.1, 1.0 and 100 µg/L of testosterone. These concentrations did not inhibit asexual reproduction but did significantly reduce the number of fertilized ovigerous females at 10 µg/L. In the marine copepod, *Acartia tonsa*, the testosterone 48-hr LC50 was 5,600 µg/L (Anderson et al. 2001). In a five day development assay, copepods were exposed from eggs until the copepodite stage and the inhibition of copepod development by testosterone was measured. The concentration reducing the number of copepods from reaching the copepodite stage by 10% (EC10) was 740 µg/L and the EC50 for development was 1,500 µg/L.

Afonso et al. (2002) exposed Chinook salmon, *Oncorhynchus tshawytscha*, to 0.1, 1.0 and 10 µg/L testosterone for 29 days post hatch. The 10 µg/L treatment was lost due to a lack of aeration but no effects were observed at 103 days post hatch on sex ratio or gonad development in fish exposed to 0.1 or 1.0 µg/L testosterone. In a similar study, Kroger et al. (2000) exposed medaka, *Oryzias latipes*, to 100 µg/L testosterone for six days as eggs (stage 10), at hatch, and at 7 and 21 days post hatch. Fish were allowed to mature and reproduce and growth, sex-ratio, gonad histology, fecundity, fertility and embryo and larval viability were assessed. Testosterone did not affect mortality, body weight, sex-ratio, or time to sexual maturity regardless of exposure period.

However, newly hatched fry or fish exposed at 1 week post hatch did display intersex gonads following 100 µg/L testosterone exposure. Testosterone exposure was also associated with an increase in the percentage of unfertilized eggs and intersex of the F1 and reduced embryo/larval survival in the F1 generation. Unfortunately, observations on these endpoints were not supported with data, thus, the magnitude of the effects cannot be assessed. In a study on an all female population of Chinook salmon, a two hour bath in testosterone concentrations up to 10,000 µg/L did not cause a significant increase in the incidence of males or intersex individuals. Hormone treatments were conducted with recently hatched fish as this has been identified as the sensitive lifestage of Chinook salmon (Piferrer et al. 1993). Other androgens tested in this assay including 11-ketotestosterone, methyldihydrotestosterone, and methyltestosterone which increased the incidence of phenotypic males at concentrations of 400, 16, and 80 µg/L, respectively.

Literature studies on the effects of testosterone on algae are limited to one study where 10,000 µg/L of testosterone inhibited algal growth in the green algae, Neospongiococcum sp. (Hardy and O'Kelly, 1986). Receptor mediated effects of testosterone on algae are not expected as testosterone is not a common constituent in algae (Mu and LeBlanc, 2002).

Considering the removal rates of testosterone in soil and sediment, measured environmental concentrations, and calculated bioconcentration factor (BCF), the applicant's conclusion that risks to the environment are unlikely from use of the patch is endorsed. It is agreed with the applicant that relatively to the endogenous testosterone production the patch will not significantly alter the concentration or distribution of testosterone, its metabolites, or degradation products in the environment. In conclusion, this extension application does not result in an increased risk to the environment.

Quality aspects

The variation application did not contain any new quality data. The product is the same as for the previously approved indication for Intrinsa.

Clinical aspects

Pharmacokinetics

The pharmacokinetic characteristics of the transdermal patch were adequately characterised in the studies included in the original submission. Pharmacokinetic results for free and total testosterone levels have also been presented in this application, based on adequate analytical methods, and other hormones have also been measured. Circulating testosterone in serum exists either tightly bound to SHBG (sex hormone binding globulin; a plasma protein synthesized in the liver that specifically binds steroid sex hormones), weakly and reversibly bound to serum albumin or as free testosterone (0.5-2%). The SHBG bound fraction is regarded as not contributing to biological activity. Factors that affect SHBG concentrations, such as concomitant estrogen therapy, also affect free testosterone concentrations.

SM and NM women have quite a similar mean baseline free testosterone level and also a similar range of individual baseline concentrations, despite the fact that SM women have no ovaries producing testosterone. Slightly higher baseline concentrations are observed in NM women, but the difference is small. Also after treatment with Intrinsa, there are no major differences between SM and NM women in the testosterone levels achieved. In general, the baseline testosterone levels increase from approximately 1 to 5 pg/ml in women on concomitant HT and from 1.6 to 5-8 pg/ml in women without concomitant HT. Both baseline and treatment levels of free testosterone are more affected by the concomitant HT than by menopausal status, which is probably due to the difference in SHBG levels. Women on oral HT have the highest SHBG concentrations and the lowest free testosterone concentrations and women on no HT have lower SHBG and higher free testosterone concentrations, while women on transdermal HT are in-between these two extremes.

The reference range for NM women could be represented by the baseline free testosterone values in the studies (1.08-1.56 pg/ml) and the achieved concentrations (4.88-5.70 pg/ml) could therefore be considered to be outside the reference range. This is further discussed in relation to the safety aspects of the widening of the indication.

Intrinsa is only available in one strength, and thus, dose proportionality is not of major importance. Results from one study roughly indicate dose proportionality over a dose range of 75 to 450 µg/day, although the exposure to free and total testosterone tended to increase slightly less than proportional. Steady state testosterone levels are generally achieved before application of the second patch. Data from phase 3 studies indicate that stable testosterone levels are achieved upon multiple dosing, with no unexpected accumulation up to 52 weeks of dosing. The inter-individual variability is moderate to high (40-50%), but this is not unexpected.

Since testosterone is a well-known endogenous substance, no specific studies have been performed in special populations but a population PK analysis included some co-variates. This analysis did not reveal any new or unexpected covariate relationships. The subjects included were healthy with respect to renal and hepatic function and very elderly patients were not included. Thus, effects of these co-variates were not to be expected. Conclusions regarding interactions with CYP3A4 inhibitors and inducers could not be drawn from the analysis.

Pharmacodynamics

No specific pharmacodynamic studies have been submitted to support this variation application. Hormone concentrations have been measured in all phase 3 studies (see above, Pharmacokinetics). As stated above, there is no clear correlation between endogenous hormone levels and female sexual function and no specific testosterone concentration has been identified as a minimum level necessary for preservation of sexual desire in women.

Clinical efficacy

Background

In the original application, Intrinsa was approved for treatment of HSDD in women who were surgically menopausal (SM) and on concomitant oestrogen treatment. In the current application, the Applicant pursues to widen the indication to include all postmenopausal women diagnosed with HSDD, regardless of concomitant hormone therapy and of type of menopause (surgical or natural). Thus, this will result in an expansion of the use of the product to a considerably larger patient population.

The clinical program to evaluate the efficacy of Intrinsa to NM and SM women with HSDD with or without concomitant HT consists of 4 Phase III, double-blind, placebo-controlled studies. These studies are summarized in Table 1.

Table 1 Clinical programme

Study	Phase/region	Design	Population	Stratification	Testosterone dose
Studies in NM women with HSDD on E+P					
2002006	III/US, Canada, Australia	24-week randomized, DB PC, efficacy and safety	NM Oral E or Oral E+P	None	0 (n=273) 300 (n=276)
2002005	III/US	24-week randomized, DB PC, efficacy and safety followed by 28 week DB,PC safety and a 3 year open label safety extension	NM Oral E or Oral E+P	None	0 (n=203) 300 (n=407)
Studies in SM or NM women with HSDD not on HT					
2004031	IIIb/US, Canada, UK, Australia	24-week randomized, DB PC, efficacy and safety followed by 28 week DB, PC safety and a 1 year single blind PC safety extension	NM or SM not on E or E+P	Menopause status (SM or NM)	0 (n=277) 150 (n=267) 300 (n=270)
Studies in NM women with HSDD not on HT or on non-CEE E					
2005108	IIIb/ Canada, UK, Sweden, Germany, Australia	24-week randomized, DB PC, efficacy and safety	NM Transdermal E or Oral non-CEE With or without P Or no E	Concomitant E use (E only, E+P, or no E or E+P	0 (n=142) 300 (n=130)

CEE= conjugated equine oestrogens; DB=double blind; E = oestrogen; HT=hormone therapy (E or E+P); P= progestagen; PC=placebo controlled, SM= surgically menopausal; NM=naturally menopausal

Efficacy was evaluated during the initial 24-week, double-blind, placebo-controlled period of each study. The diagnostic instruments used to assess sexual function are the same as in the original Intrinsa application and appear to be well developed for the purpose of the studies. Patients enrolled in all the 4 studies satisfied the same diagnostic criteria and similar inclusion and exclusion criteria as patients in the original trials in SM women with HSDD who were receiving HT. In all 4 studies, the patients were healthy women, aged 40 – 70 years for NM or 20-70 for SM women, who met the diagnostic criteria for acquired HSDD, were in stable relationships in which partner factors would not preclude the possibility of demonstrating a treatment effect, and who did not have any breast or cervical malignancies at baseline.

The primary endpoint in all 4 studies was the change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes (SAL). Secondary endpoints included the change from baseline to week 24 in the sexual desire domain of the PFSF and the change in personal distress, (PDS). Other important secondary endpoints were the changes in the other PFSF domains. These are the same primary and secondary endpoints that were used in the original evaluation and are considered adequate to evaluate efficacy of the treatment.

Because of previously observed effects of high SHBG on efficacy, the primary analysis population for Studies 2002005 and 2002006 was defined *a priori* to include patients whose SHBG levels were ≤ 160 nmol/L. Secondary analyses were to be performed in the intent-to-treat (ITT) population.

Studies 2004031 and 2005108 enrolled women who were not receiving HT or who were receiving only non-CEE forms of HT; the populations in these studies were expected to have generally lower SHBG levels than the populations in studies with high levels of oral CEE use. Therefore, the primary analysis population in these studies was defined to be the ITT population.

The withdrawal rates were 20-29% in the groups treated with Intrinsa in 3 of the 4 studies. In study 2004031, the rate was 40%, but this was over the entire 52 week study duration. The withdrawal rate at week 24 was similar to the other studies.

Study results

- **Study 2002006**

Primary endpoint SAL
A statistically significant increase was obtained for the primary endpoint SAL in the Intrinsa group compared with placebo at week 24. These results were supported by the analysis in the per protocol population using the *t* test (mean difference = 1.06; p = 0.0023).

Table 2 4-week frequency of total satisfying episodes (SAL) at week 24 (LOCF) in ITT population

				Change from baseline			
	N	Baseline Mean (SE)	Week 24 (LOCF) Mean (SE)	Mean (SE)	Median (P25, P75)	Difference CI	T-test P value
Placebo Intrinsa	269 270	2,80 (0,17) 2,64 (0,15)	3,35 (0,26) 4,56 (0,31)	0,54 (0,21) 1,92 (0,26)	0,0 (-1,0, 1,5) 0,7 (0,0, 3,1)	1,38 (0,72, 2,03)	<0.0001

Responder Analysis
A responder was prospectively defined (based on a previous study) as a patient who had increases from baseline of >1 episode in the SAL per 4-week period. Using this definition of a responder, in the Intrinsa group, 43% responded to treatment compared with 27% in the placebo group (p < 0.0001) using ITT patients. Responder analysis using other cut-off values (i.e. >0, >2, >3 episodes per 4-week period) to define responders were explored.

Table 3 4-week frequency of total satisfying episodes at week 24 (LOCF): Responder analysis using different cut-off values ITT population

Cut-off	Placebo (n=269)	Intrinsa (n=270)	p-value
>0	108 (40,1%)	158 (58,5%)	<0.0001
>1	73 (27,1%)	117 (43,3%)	<0.0001
>2	51 (19,0%)	84 (31,1%)	0.0011
>3	33 (12,3%)	69 (25,6%)	<0.0001

Subgroup analyses
The effect of Intrinsa compared with placebo was analysed across subgroups (i.e. patients categorized by disease severity, hormone concentrations, demographic and reproductive characteristics etc) in ITT patients with regard to the mean changes from baseline in the frequency of total satisfying episodes (SAL) at week 24. For most subgroups, a greater mean change from baseline was observed in the Intrinsa group compared with placebo. However, there was no difference between Intrinsa and placebo in non-caucasian women, in women whose BMI exceeded 30, in women with SHBG >160nmol/l, in women on Premarin and on non-Premarin oral non-oestradiol.

- **Study 2002005**

Primary endpoint SAL
The analysis did not show a statistically significant difference between Intrinsa and placebo groups in the primary efficacy endpoint (change in 4-week frequency of total satisfying episodes at week 24, SAL) for the primary efficacy population nor for the ITT population, who had baseline SHBG serum concentrations ≤160 nmol/L.

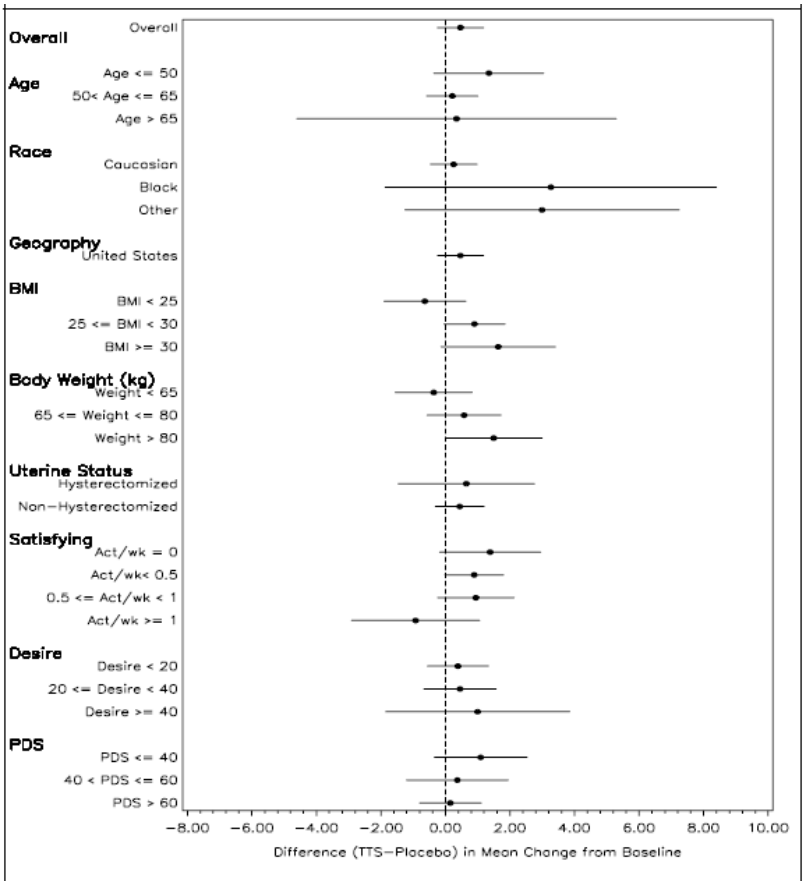
Table 4 4-week frequency of total satisfying episodes (SAL) at week 24 (LOCF) in ITT population with SHBG <=160nmol/l

			Unadjusted change from baseline				
	N	Baseline Mean (SE)	Mean (SE)	Median (P25, P75)	Difference in means (CI)	WRS p-value	T-test p-value
Placebo	186	2,70 (0,25)	1,39 (0,49)	0,0 (-0,6, 1,8)	-0,01 (0,99, 0.96)	0,1371	<0.1371
Intrinsa	355	3,26 (0,24)	1,38 (0,25)	0,7 (-0,7, 2,7)			

Responder analysis SAL
A responder was prospectively defined as a patient who had increases from baseline of > 1 episode in the SAL per 4-week period. No statistically significant difference in the primary efficacy endpoint SAL was observed between the treatment groups in the percentage of patients who responded to treatment in the primary analysis population (40.0% in the Intrinsa group versus 32.8% in placebo; p = 0.1005).

Subgroup analysis

The effect of Intrinsa was compared with placebo across various subgroups.



- **Study 2004031**

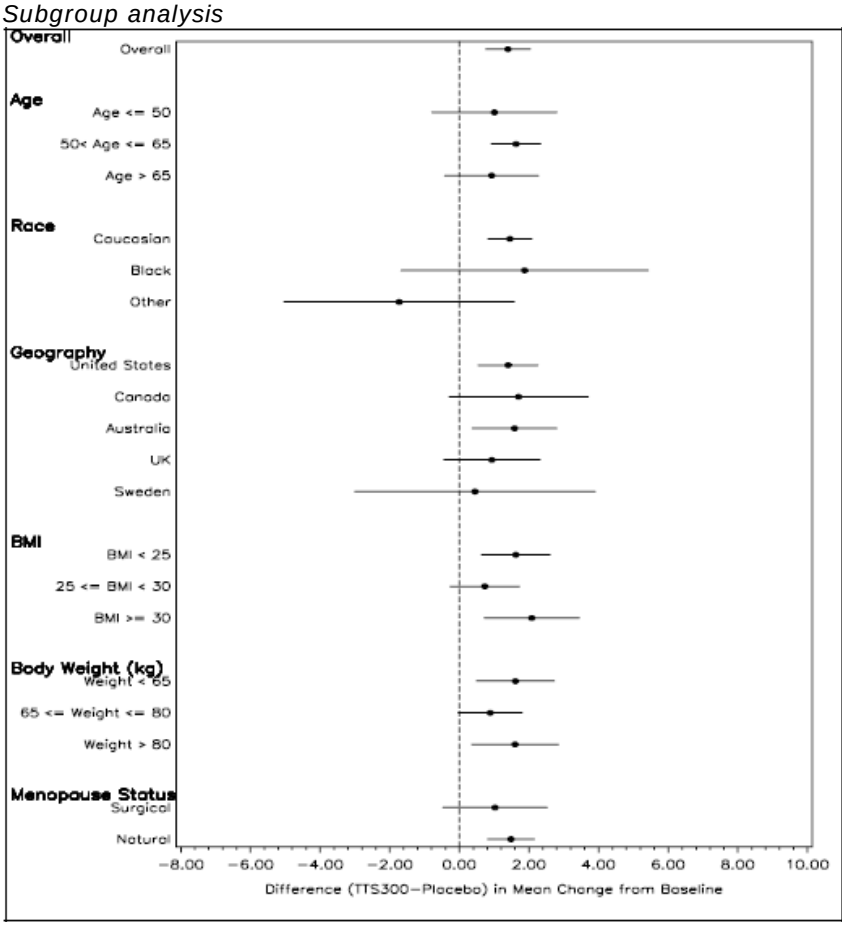
Primary endpoint SAL
A statistically significant difference in treatment effect compared with placebo for the primary efficacy endpoint as measured by the SAL at 24 weeks was observed for 300 mcg/day testosterone but not for 150 mcg/day testosterone. Women receiving 300mcg/day testosterone experienced a mean increase of 2.12 total satisfying episodes per 4 week period compared to a mean increase of 0.73 total satisfying episodes per 4 week period for those receiving placebo.

Table 5 4-week frequency of total satisfying episodes (SAL) at week 24 (LOCF) in ITT population Winsorized

				Change from baseline			
	N	Baseline Mean (SE)	Week 24 (LOCF) Mean (SE)	Mean (SE)	Median (P25, P75)	Difference CI	ANOVA P value
Placebo	265	2,49 (0,16)	3,24 (0,22)	0,73 (0,19)	0,0 (-1,0, 2,0)		
Intrinsa 150	252	2,86 (0,23)	4,00 (0,28)	1,18 (0,22)	0,3 (-0,7, 2,7)	0,46 (-0,12, 1,03)	0,1102
Intrinsa 300	254	2,42 (0,17)	4,50 (0,30)	2,12 (0,26)	1,0 (0,0 , 3,8)	1,40 (0,76, 2,03)	<0.0001

Responder analysis SAL
A responder was prospectively defined as a patient who had increases from baseline of >1 episode per 4-week period. A significantly higher percentage of patients in the 300 mcg/day testosterone group responded to treatment compared with placebo (46.5% for 300 mcg/day testosterone versus 31.7% for placebo; p < 0.0006).

Subgroup analysis



- **Study 2005108**

Primary endpoint SAL
For the primary efficacy endpoint of change from baseline in 4-week SAL, a statistically significant benefit of 300 mcg/day testosterone compared with placebo was observed.
Women receiving 300mcg/day testosterone experienced a mean increase of 1.69 total satisfying episodes per 4 week period compared to a mean increase of 0.53 total satisfying episodes per 4 week period for those receiving placebo

Table 6 4-week frequency of total satisfying episodes (SAL) at week 24 (LOCF) in ITT patients (Winsorized)

				Change from baseline			
	N	Baseline Mean (SE)	Week 24 (LOCF) Mean (SE)	Mean (SE)	Median (P25, P75)	Difference CI	Koch´s P value
Placebo	128	2,14 (0,22)	2,74 (0,29)	0,53 (0,26)	0,0 (-1,0, 1,6)	1,15 (0,33, 1,98)	0,0089
Intrinsa	119	2,50 (0,26)	4,24 (0,39)	1,69 (0,34)	1,0 (0,0, 3,0)		

Responder analysis
A responder was prospectively defined as a patient who had increases from baseline of >1 episode per 4-week period. A significantly higher percentage of patients in the Intrinsa group responded to treatment compared with placebo (57% in the Intrinsa group versus 43% in placebo; p = 0.0279).

Subgroup Analysis
When analyzed with regard to concomitant HT or not, a statistically significant treatment effect for SAL per 4 weeks was observed in the subgroup with no concomitant E or E+P.

Table 7 4-week frequency of total satisfying episodes (SAL) at week 24 (LOCF) by subgroup in ITT patients (Winsorized)

					Change from baseline			
Concomitant HT		N	Baseline Mean (SE)	Week 24 (LOCF) Mean (SE)	Mean (SE)	Median (P25, P75)	Difference CI	Koch´s P value
No E or E+P	Placebo	93	2,11 (0,27)	2,61 (0,31)	0,59 (0,28)	0,0 (-0,7, 1,8)	1,23 (0,23, 2,22)	0,0193
	Intrinsa	87	2,25 (0,26)	4,12 (0,44)	1,81 (0,42)	1,0 (-0,2, 3,3)		
E or E+P	Placebo	35	2,13 (0,35)	2,95 (0,63)	0,72 (0,74)	0,0 (-1,3, 1,4)	0,82 (-099, 2,62)	0,2089
	Intrinsa	32	3,11 (0,63)	4,64 (0,84)	1,53 (0,56)	1,6 (0,0, 2,4)		

Clinical safety

In the double-blind period of the 9 combined Phase IIb/III studies, 2794 patients were exposed to Intrinsa, for a total of 1913 patient-years; 297 patient-years of which (16%) were in SM women receiving concomitant E (the original patient population), 545 (28%) were in NM women receiving concomitant HT, and 1071 (56%) were in menopausal women not receiving concomitant HT. Overall, 2267 patients were exposed for at least 6 months, 1231 patients for at least 1 year, and 45 patients for at least 2 years.

In open-label trials, 55 patients have been exposed for at least 48 months. The overall safety data base is based on double-blind and open-label periods of phase IIb/III studies in which 3306 patients have been exposed.

Table 8

S-Table 7
Exposure to TTP 300 by Menopausal Type and Hormone Therapy (HT) Use:
Double-blind and Open-label Periods of Phase IIb/III Studies
(Intent-to-treat)

Duration of Exposure (# of Patients)	SM on E	NM on HT	SM/NM not on HT	Total
>0 Weeks (total number of patients)	1114	920	1272	3306
>22 Weeks (6 Months)	872	751	1053	2676
>50 Weeks (12 Months)	473	431	842	1746
>76 Weeks (18 Months)	248	226	62	536
>102 Weeks (24 Months)	177	194	45	416
>128 Weeks (30 Months)	132	138	0	270
>154 Weeks (36 Months)	110	102	0	212
>180 Weeks (42 Months)	84	49	0	133
>206 Weeks (48 Months)	43	12	0	55
Total exposure (patient months)	14016	12053	12854	38923
Total exposure (patient years)	1168	1004	1071	3244
Average exposure (months)	12.6	13.1	10.1	11.8

Includes double-blind and open-label data from Studies 1999068, 1999092, 2001133, 2001134, 2002005, 2002006, 2004031, 2005108, and 2007004.
NM=naturally menopausal; SM=surgically menopausal; E=estrogen; p=progestin.
TTP = testosterone transdermal patch (mcg/day).
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There were no major differences between SM and NM women in the testosterone levels achieved. In general, the baseline testosterone levels increased from approximately 1 pg/ml to 5 pg/ml in women on concomitant HT and from 1.6 to 5-8 pg/ml in women without concomitant HT. Both baseline and treatment levels of free testosterone are more affected by the concomitant HT than by menopausal status, which is probably due to the difference in SHBG levels. Women on oral HT have the highest SHBG concentrations and the lowest free testosterone concentrations and women on transdermal HT or no HT have lower SHBG and higher free testosterone concentrations.

Common adverse events
The most common adverse event was application site reactions, which were observed in 34.5% of placebo patients and in 27.7% of patients treated with Intrinsa. Application site reactions are a common adverse event with all patch treatments. The reaction is assessed to be caused by the pharmaceutical composition of the patch, not enhanced by the active ingredient testosterone. The adverse event did not increase with increasing duration of treatment, and no increase in frequency of skin sensitization was noted when investigated in the combined, double-blind trials.

Table 9 Adverse events at >=2% and higher incidence in Intrinsa 300 than placebo by Medra system organ class

S-Table 12
Adverse Events at >=2% and Higher Incidence in TTP 300 Than Placebo by MedDRA System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT): Double-blind Period of Phase IIb/III Studies (Intent-to-treat)

MedDRA SOC/HLT/PT	Placebo (N=1848) n (%)	Placebo nAE	TTP 300 (N=2794) n (%)	TTP 300 nAE	RR (95% CI)
Infections and infestations					
Lower respiratory tract and lung infections	61 (3.3%)	70	93 (3.3%)	106	1.2 (0.8, 1.6)
Urinary tract infections	61 (3.3%)	74	115 (4.1%)	139	1.3 (0.9, 1.8)
Urinary tract infection	48 (2.6%)	55	83 (3.0%)	101	1.2 (0.8, 1.8)
Injury, poisoning and procedural complications	136 (7.4%)	169	210 (7.5%)	258	1.0 (0.8, 1.3)
Investigations	113 (6.1%)	138	207 (7.4%)	260	1.1 (0.9, 1.4)
Physical examination procedures	40 (2.2%)	40	89 (3.2%)	89	1.2 (0.8, 1.9)
Weight increased	36 (1.9%)	36	87 (3.1%)	87	1.3 (0.8, 2.0)
Metabolism and nutrition disorders	32 (1.7%)	33	61 (2.2%)	62	1.2 (0.8, 1.9)
Reproductive system and breast disorders	208 (11.3%)	291	327 (11.7%)	426	1.0 (0.8, 1.2)
Vulvovaginal signs and symptoms	36 (1.9%)	40	73 (2.6%)	89	1.3 (0.9, 2.0)
Respiratory, thoracic and mediastinal disorders					
Coughing and associated symptoms	33 (1.8%)	39	56 (2.0%)	58	1.3 (0.8, 2.0)
Cough	33 (1.8%)	38	56 (2.0%)	58	1.3 (0.8, 2.0)
Skin and subcutaneous tissue disorders	377 (20.4%)	503	595 (21.3%)	856	1.2 (1.1, 1.4)
Acnes	86 (4.7%)	94	149 (5.3%)	161	1.5 (1.1, 1.9)
Acne	86 (4.7%)	94	148 (5.3%)	160	1.5 (1.1, 1.9)
Hypertrichoses	122 (6.6%)	148	252 (9.0%)	322	1.7 (1.3, 2.0)
Hirsutism	122 (6.6%)	148	252 (9.0%)	322	1.7 (1.3, 2.0)
Vascular disorders					
Vascular hypertensive disorders NEC	35 (1.9%)	36	62 (2.2%)	63	1.0 (0.7, 1.6)
Hypertension	35 (1.9%)	36	62 (2.2%)	63	1.0 (0.7, 1.6)

Studies 1999092, 2001133, 2001134, 2002006, and 2005108 (Weeks 0-24) and Studies 1999068, 2002005, and 2007004 (Weeks 0-52) and Study 2004031 (Weeks 0-104).
RR (95% CI) = Relative Risk and 95% confidence interval (adjusted by study).
TTP = testosterone transdermal patch (mcg/day).
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The second most common adverse event was upper respiratory infection, assessed as not related to treatment. Increased hair growth, which is an androgenic effect, was the third most common adverse event.

Effect on weight gain
Treatment with Intrinsa induced weight gain to a higher incidence than in the placebo group, assessed as most probably related to drug treatment. Whether the increase in weight is in fat or non-fat (lean) mass is unknown.

Androgenic adverse events
Adverse events known to be associated with increased androgen levels or androgen excess in women include acne, alopecia, increases in body or facial hair (hirsutism), voice deepening, and clitoromegaly.

Treatment with Intrinsa did not increase the risk of developing alopecia or deepening of the voice.

Acne is an expected androgenic adverse event considered related to drug treatment and was more often seen in patients treated with Intrinsa (5.5%) compared to placebo treated patients (4.9%). The risk of developing acne did not increase with increasing duration of the clinical studies.

Treatment with Intrinsa increases the risk of developing increased facial hair growth, which was observed in 9% in Intrinsa treated patients versus 6.6% in the placebo group. Most of the events were classified as mild and only a few patients withdrew due to increased hair growth events. However, the withdrawal rate was higher in the Intrinsa group (0.7%) vs. placebo (0.3%). The relative risk of increased acne and facial hair were similar in this variation population compared to the original population of patients. As could be expected, there were a statistically significant association between the incidence of acne and increased hair growth and the mean serum free testosterone level.

An increased incidence of enlarged clitoris was observed in patients treated with Intrinsa (0.5%; 13 out of 2794 patients) compared with placebo (<0.1%; 1 out of 1848 patients) and was more often seen in long term studies (12 and 24 month studies) compared to studies with shorter duration. The issues related to androgenic adverse events should be followed in the Risk Management Plan.

Breast safety
The breast is a target organ for sex steroids and hormonal treatments have been found to increase the risk for breast cancer. A majority of the patients on Intrinsa with invasive and in-situ breast cancer had been on oral contraceptive or were using hormone replacement therapy, and the assessor concluded that the patients had been exposed to oestrogen. The potential increase in risk with Intrinsa alone is difficult to evaluate from the performed clinical trials, and should carefully be followed in the Risk Management Plan.

Mammographic breast density is related to increased risk for breast cancer. With Intrinsa alone there was no statistically significant change from baseline to week 52 in the percentage of breast density compared to placebo in women without hormone replacement therapy.

In the presented data there was no effect on proliferation from Intrinsa, but a significant increase in proliferation in patients on oestrogen and progestin therapy. The result on proliferation in Intrinsa group was reassuring, but limited for prediction of breast cancer risk during long term treatment. However, published observational studies and *in vitro* data indicate that there is no consensus on an increased risk of breast cancer in postmenopausal women using testosterone.

Endometrial safety
No endometrial cancers were reported in the clinical trial program. However, these results are too limited to be predictive of endometrial cancer risk following long-term treatment which should be closely followed in the Risk Management Plan.

Ovarian safety
Few ovarian adverse events were observed following treatment with Intrinsa in the natural menapausal women. The most common events were simple cysts, which were usually detected during the annual transvaginal ultra sound evaluations rather than during the bimannual examination. For this application which includes women with remaining ovaries, there is no evidence of adverse effects of Intrinsa treatment during short-term therapy, but long-term safety has to be followed in the Risk Management Plan.

Cardiovascular safety
No cardiovascular safety risks were identified during short-term treatment with Intrinsa. As testosterone is a potent hormone which is attributed to have negative effects on the cardiovascular system in men, there is concern with regard to long-term cardiovascular safety also in women, which would not be expected to be apparent in the limited short-term database available.

The short-term safety data obtained in the studies submitted in this variation application have not revealed any unexpected findings. When the safety data from all 9 studies were pooled, the overall adverse event profile, including data from the new studies in NM women, was very similar to the profile previously established in SM women. However, there are serious concerns related to the long-term safety aspects of testosterone in women.

Long term safety
Currently, long term safety data (i.e. more than 2 years exposure) for treatment with Intrinsa in women with NM is very limited, particularly for women not on hormone therapy (n=45 for more than 2 years exposure). Although available data do not suggest any cardiovascular risk, invasive breast cancer risk, ovarian cancer or endometrial cancer/hyperplasia risk with Intrinsa in the different subpopulations investigated, the data do not remove the safety concern.

Pharmacovigilance system

Risk Management Plan

Safety specification:
The Identified and potential risks and the Important missing information have been described. Androgenic adverse events were included as Important identified risks. Breast cancer, cardiovascular disease and endometrial cancer were included as Important potential risks.

Pharmacovigilance Plan:
All ongoing studies and activities that were part of the SM indication Pharmacovigilance Plan (such as the EMPOWER, THIN and PEM studies) will be expanded to address the respective safety concern in the extended indication of menopausal women.

Risk minimisation
Risk minimisation measures were described for the different safety concerns. Routine Risk minimisation activities were considered to be sufficient for all safety concerns.

Table 10 Summary of the EU Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Important Identified Risks • Androgenic adverse events	• Routine pharmacovigilance activities and pharmacovigilance activities specific to the product • Stimulated Reporting by sales representatives • Follow-up for reversibility in the Prescription Event Monitoring Study • Follow-up of specific androgenic adverse events (clitoromegaly and severe voice deepening) in the EMPOWER study to determine resolution. • Outcomes of Women Using Testosterone: A Follow-up Study with the THIN and GPRD Databases in the UK	SPC and PIL information regarding risk of androgenic adverse events and to consider discontinuation if deemed warranted.
Important Potential Risks 1. Breast cancer 2. Cardiovascular (CV) disease 3. Endometrial cancer	• Routine Pharmacovigilance activities and Pharmacovigilance activities specific to the product[1,2,3] • Review of ongoing studies[3] • Non-interventional prospective observational study (EMPOWER)[1,2] • Outcomes of Women Using Testosterone: A Follow-up Study with the THIN and GPRD Databases in the UK[1,2,3]	1. Detailed information in SPC Section 4.4. 2. Detailed information in SPC Section 4.4. 3. Detailed information in SPC Section 4.4.
Important missing information • Long term safety for rare events in the target population (potential risks) • Actual Post-Authorisation Usage - Use by populations not covered by SPC	• Routine Pharmacovigilance activities and Pharmacovigilance activities specific to the product. • Non-interventional prospective observational study (EMPOWER). • Outcomes of Women Using Testosterone: A Follow-up Study with the THIN and GPRD Databases in the UK	See points 1-3 above.
[1,2,3] refer to the respective potential safety concern		

Overall discussion and benefit-risk assessment

Background

Intrinsa is currently approved for treatment of HSDD in women who are surgically menopausal and on concomitant oestrogen treatment (HT). The company has applied for an extended indication to include menopausal women with HSDD regardless of menopausal state, i.e. both naturally menopausal (NM) and surgically menopausal (SM), and regardless of concomitant HT.

Beneficial effects

In postmenopausal women diagnosed with HSDD, regardless of type of menopause (surgical or natural), the comprehensive results suggest a modest but statistically significant effect of Intrinsa over placebo, despite the fact that one of the 3 clinical studies did not show a statistically significant difference over placebo for the primary endpoint SAL.

The magnitude of the beneficial effect corresponds to a mean change from baseline of around or less than 2 satisfying sexual episodes (SAL) in a 4-week period. In terms of responder rates, the difference compared to placebo for both primary and secondary endpoints was 12 – 15%. These effects may seem modest but are similar to the effects accepted by the CHMP in the approval of the application for SM women on concomitant HT, and there is no reason to neither anticipate nor require larger effects in NM women.

Risks

Exogenous testosterone exposure to otherwise healthy women with intact ovaries, creates specific concerns regarding long-term cardiovascular risks and reproductive cancer risk. Although an additive effect of applying exogenous testosterone may not result in mean testosterone levels outside the "normal" range, it cannot be dismissed that this may expose individual women to a potential risk that is difficult to assess.

Short Term Risks

The adverse event profile demonstrated in the 4 trials in surgically menopausal women that formed the basis for the original approval for marketing has not substantially changed when the studies submitted in the current application have been added to the integrated safety data set. The most common adverse event was application site reactions, which were observed in 34.5% of placebo patients and in 27.7% of patients treated with Intrinsa. Androgenic adverse events, e.g. acne, alopecia, increases in body or facial hair (hirsutism), voice deepening and clitoromegaly are expected for this kind of product and have been reported in the studies.

Long Term Risks

No endometrial cancers were reported in the clinical trial program. Based on the limited safety data base available, there is no indication of an increased risk of endometrial hyperplasia/cancer, nor of uterine fibroids in the different subpopulations investigated. However, the development of endometrial hyperplasia and cancer takes long time and a potentially increased risk induced by long-term testosterone therapy cannot be ruled out based on available data.

Already at the time of the original application, it was concluded that long-term safety of treatment with testosterone was little studied and this created concerns with regard to cardiovascular and breast safety. Therefore, different risk management activities were listed in the RMP, including post-marketing non-interventional studies (EMPOWER, PEM and THIN studies). The recruitment in these studies has so far been rather slow. Thus, currently there is no available additional information concerning long- term safety for patients covered by the already approved indication. Based on previous experience, it is evident that RMP activities and further proposed post-marketing studies in the new population may not provide the required long term data.

As the proposed indication widens the target population and as a result of potentially increased testosterone levels in women with intact ovaries, new safety concerns were identified. Currently, long term safety data (i.e. more than 2 years exposure) for treatment with Intrinsa in NM women is very limited, particularly for women not on hormone therapy. Although available data do not suggest any cardiovascular risk, invasive breast cancer risk, ovarian cancer and endometrial cancer/hyperplasia risk with Intrinsa in the different subpopulations investigated, the data do not remove the safety concern as the baseline population is far too small and the duration of exposure far too limited to allow safety conclusions. Prospective long term data from a large number of patients could have provided reliable conclusions on the safety of hormonal treatment in the extended population, but such data are not available.

The MAH refers to published studies regarding exogenous testosterone use and the risk of breast cancer. The results from the studies are conflicting and inconclusive; however, do not indicate a markedly increased risk of breast cancer related to testosterone.
It must be concluded that the long-term safety risks with testosterone treatment in women with intact ovaries - the proposed target population of this variation - cannot be meaningfully evaluated based on the documentation submitted by the MAH and, therefore, the safety issue cannot be considered resolved.

Benefit-risk balance

The results of the submitted studies suggest that some post-menopausal women with HSDD could expect a modest improvement by treatment with Intrinsa.

The widening of the indication to include all post-menopausal women with HSDD would imply a considerably increased target population for which there still are potential serious long- term safety concerns. The available long- term safety data of treatment with Intrinsa is still considered limited and not robust enough to support a positive benefit/risk balance in the proposed target population.

Conclusion

The benefit/risk balance is considered negative for the proposed indication.