SHORT COMMUNICATION

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Drug Utilization of Intrinsa® (Testosterone Patch) in England

Interim Analysis of a Prescription-Event Monitoring Study to Support Risk Management

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Abstract

Background: Intrinsa® is a transdermal testosterone patch that is indicated for use in hypoactive sexual desire disorder (HSDD) in women who have undergone bilateral oophorectomy and hysterectomy (surgically-induced menopause) receiving concomitant oestrogen therapy.

Objective: To describe the utilization characteristics of the patients prescribed testosterone patch (Intrinsa®) based on an interim analysis of an ongoing Prescription-Event Monitoring study in England, and to assess, where possible, if the product is being used within the licensed therapeutic indication.

Methods: In this interim analysis, patients were identified from dispensed prescriptions that had been issued by general practitioners (GPs) for Intrinsa® from March 2007. 'Green form' questionnaires were sent to GPs 6 months following the date of the first prescription for Intrinsa® for each individual patient, requesting information including age, sex, start and stop dates of treatment (if stopped), prescribing indication and reasons for stopping. Additional questions were asked regarding the patient's menopausal status and use of concomitant oestrogen therapy.

Results: The interim cohort consisted of 756 patients. The majority of patients were reported to be female (746 [98.7%]) with a median (interquartile range) age of 50 years (44–55 years). The most commonly reported indication was the licensed indication of HSDD in 580 patients (76.7%). Just under one-half of the patients (n = 364 [48.1%]) were reported to have been hysterectomized and bilaterally oophorectomized (surgically-induced menopause) prior to starting Intrinsa®; 127 patients (16.8%) were naturally menopausal. For 222 patients (29.4%) the GP specified that the patient was not using concomitant oestrogen therapy. Overall, only 219 patients (29.0%) in the cohort were being prescribed Intrinsa® according to the manufacturer's recommendations.

Conclusions: This study has highlighted that some clinicians are prescribing this product outside the recommended terms of the licence, with less than 30% of patients receiving Intrinsa® according to prescribing guidelines. All events

experienced by these patients will be analysed to detect any possible adverse events from using Intrinsa® outside of the licensed therapeutic indication. The findings support the ongoing postmarketing risk management of the product.

Background

Intrinsa®[1] is a transdermal testosterone patch that is indicated for use in hypoactive sexual desire disorder (HSDD) in women who have undergone bilateral oophorectomy and hysterectomy (surgically-induced menopause) receiving concomitant oestrogen therapy.[1] European Public Assessment Reports (EPARs) are summaries of the scientific conclusions reached by the Committee for Medicinal Products for Human Use (CHMP) at the end of the centralized evaluation process of new drugs, based on documentation of the pre-marketing development programme by the manufacturer. HSDD is defined within the EPAR for Intrinsa® as "A deficiency or absence of sexual fantasies and sexual desire for sexual activity. The disturbance must cause marked distress or interpersonal difficulty and must not be better accounted for by another psychological disorder or condition".[2] The efficacy of testosterone delivered by a transdermal patch in surgically menopausal women has been demonstrated in a number of randomized controlled trials.[2-7] Each Intrinsa® testosterone patch provides 300 μg testosterone/day, which is consistent with testosterone production in premenopausal women (100–400 μg testosterone/day).[1] Intrinsa® must be used in conjunction with oestrogen therapy and continued use is only recommended while concomitant oestrogen is considered appropriate.[1] Use of Intrinsa® concomitantly with conjugated equine oestrogen treatment is included as a special warning within the summary of product characteristics (SPC), as efficacy has not been demonstrated.[1] Clinical trials have been published on the use of the testosterone patch in naturally menopausal women and in women not taking concomitant oestrogen therapy; however, long-term safety information for these patient populations is still unknown.[1,8,9]

After the launch of a medicinal product, it may be used in populations that differ from those examined in clinical trials.[10] This may result in the product being used in populations where there are known, potential or unknown risks. The safety specification for a product will outline these risks and form the basis of the evaluation for the need for risk minimization activities.[11] The manufacturer can address potential risks by planning necessary pharmacovigilance action and including these in the risk management plan (RMP) of the product. An RMP identifies any known or potential risks associated with the product and any missing information relevant to the safety of the product. When required, the RMP includes strategies for risk minimization to reduce identified and potential risks. As such, risk management strategies can be focused on minimizing the risks of medicinal products by monitoring use in populations that may be at risk.[11] A specific concern in relation to the use of the testosterone patch is that there is little long-term safety data (>52 weeks), which is important in relation to the potential risk of breast cancer, as well as the potential risk of endometrial cancer in non-hysterectomized women.[2] Additionally, Intrinsa® is only recommended for surgically menopausal women up to the age of 60 years. There is limited data on patients over the age of 60 years, which is consistent with the prevalence of HSDD.[1] Patients who may become pregnant (premenopausal women) should not use Intrinsa® as testosterone can have an adverse affect on the fetus.[1]

Prescription-Event Monitoring (PEM) is a pharmacoepidemiological tool that can be used to examine the safety of newly marketed drugs in general practice.[12] PEM data also provide

1 The trade name Intrinsa® is used for product identification purposes to distinguish it from other testosterone patch products.

important utilization characteristics on patients who have been prescribed the product, and can be used to examine whether prescribing guidelines are being adhered to.

The objective of this study is to describe the utilization characteristics of patients prescribed testosterone patch (Intrinsa®) based on an interim analysis of an ongoing PEM study and to assess, where possible, if the prescribing guidelines are being followed.

Methods

A PEM study was conducted to monitor the safety of Intrinsa® as used in general practice in England. A detailed description of PEM is published elsewhere.[12] Patients were identified from dispensed prescriptions that had been issued by general practitioners (GPs) for Intrinsa®. The GPs were sent a 'green form' questionnaire at least 6 months following the date of the first prescription for Intrinsa® for each individual patient, requesting information including start and stop dates of treatment (if stopped), age, sex, suspected adverse drug reactions, reasons for stopping Intrinsa® and details of events[2] experienced by patients after starting therapy. GPs were also asked whether the patient was hysterectomized and bilaterally oophorectomized prior to starting Intrinsa® and, if not, to specify whether they were hysterectomized only, bilaterally oophorectomized only, naturally menopausal or premenopausal. In addition, details of concomitant oestrogen products were requested.

Patients were included in this analysis if a questionnaire containing clinical information was returned up to the end of November 2008; Prescription information was collected from the date of market launch (March 2007). The green form information for these patients was coded and then extracted from the database. All events reported on green form questionnaires were coded onto a DSRU database using the DSRU Event Dictionary. This hierarchical dictionary, which is arranged in a system-organ classification, groups associated 'doctor summary terms' (terminology used by the prescribing physician) under lower-level event terms; similarly, related lower-level event terms are grouped under a broader term (higher-level term). Analyses were performed using Stata V10 (StataCorp, College Station, TX, USA).

Off-label use was examined in respect to indications other than HSDD, patients not hysterectomized and bilaterally oophorectomized, patients not using concomitant oestrogen therapy and any reported use in male patients. Additionally, warnings and precautions for use were examined, including use in women aged ≥60 years, naturally menopausal women and patients using conjugated equine oestrogen products.

Analysis

Summary statistics of the characteristics of the cohort were calculated. Where the data were stratified by menopausal status, differences between categorical variables were tested using Pearsons chi-squared test, and differences between continuous variables were tested using parametric two-sample Student's t-tests, where appropriate. The proportion of patients within the interim cohort who were concordant with the prescribing guidelines was summarized through the construction of a simple profile score assembled using the algorithm shown in figure 1.

Ethics

This (ongoing) PEM study is conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the CIOMS in collaboration with the WHO (2002).[13] The method of study also complies with the Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College

2 An 'event' in Prescription-Event Monitoring is defined as 'any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's notes.'

Sex		Indication		Menopausal status		Therapy	Total score
Female = 1	+	HSDD = 1	+	Hysterectomized and bilaterally oophorectomized = 1	+	Concomitant oestrogen therapy = 1	Maximum = 4
Male = 0		Others = 0		Other = 0		Other = 0	Minimum = 0

Fig. 1. Summary of algorithm for determining patients' profile score and concordance with prescribing guidelines. **HSDD** = hypoactive sexual desire disorder.

of Physicians.[14] In addition, PEM is mentioned in the 'Frequently Asked Questions' section of the General Medical Council booklet 'Confidentiality: Protecting and Providing Information', as ''a professional organization that monitors the safety of medicines to which doctors should provide relevant information from patients' records wherever possible''.[15]

Quality Assurance in PEM

Good data management is a high priority in PEM. A number of strategies exist to minimize biased results. Data quality is assured through a number of methods such as operator training, on-screen validation during data entry, adoption of and adherence to study-specific data coding conventions, coding and convention meetings, double entry (10%) with error reporting, data cleaning using logical checks and analysis of outliers, and a study-specific analysis design that includes imputations for missing, illogical and conflicting data as reported on the study questionnaire. Data for this interim analysis has been subject to all the aforementioned processes, with the exception of systematic data cleaning and imputation, which is routinely undertaken at study completion. Thus, results are estimates that may change subsequent to further data cleaning. However, if any data errors have been identified during the conduct of this interim analysis, the database has been updated accordingly.

Results

Interim Cohort Characteristics and Off-Label Use

At the time of this interim analysis, green form questionnaires had been returned for 820 patients. There were 64 questionnaires classified as invalid (7.8% of returned questionnaires). Data is presented in this study for an interim cohort consisting of 756 patients. Off-label use is summarized in table I, and use contravening warnings and precautions for use, as listed in section 4.4 of the SPC,[1] are summarized in table II. These tables provide data on subsets of patients who fall into these categories, therefore not all patients will be featured in these.

Age and Sex

The interim cohort comprised 746 females (98.7% of the cohort), 8 males (1.1%) and 2 patients (0.3%) in whom the sex was not specified; however, both the latter patients had an indication of HSDD and were reportedly premenopausal.

The median age of the female patients was 50 years (interquartile range [IQR] 44–55 years) with a range between 25 and 72 years. Intrinsa® is only indicated up to the age of 60 years because of

Table I. Off-label use of Intrinsa® in the interim Prescription-Event Monitoring cohort

Off-label use	No. of patients (percentage of cohort)[a]
Indications other than HSDD	133 (17.6)
Indications other than 'decreased libido'[b]	94 (12.4)
Patients not hysterectomized and bilaterally oophorectomized[c] (i.e. at potential risk of endometrial cancer and adverse effects on female fetus if pregnant)	254 (33.6)
Patients not using concomitant oestrogen therapy	222 (29.4)
Use in male patients	8 (1.1)

a These data were derived from various variables and the counts are not mutually exclusive.

b Includes the 'Dr Summary' term for HSDD from the Drug Safety Research Unit dictionary.

c Excluding those that were conflicting or unspecified.

HSDD = hypoactive sexual desire disorder.

Table II. Use contravening the warnings and precautions for use of Intrinsa®, from section 4.4 of the SPC[1] in the interim Prescription-Event Monitoring cohort

Warnings and precautions for use	No. of patients (percentage of cohort)[a]
Use in women aged ≥60 years	80 (10.7)
Naturally menopausal women (i.e. at potential risk of endometrial cancer)	127 (16.8)
Patients using conjugated equine oestrogen	42 (5.6)

a These data were derived from various variables and the counts are not mutually exclusive.

limited data on its use in patients beyond this age;[1] however, there were 80 female patients (10.7%) aged 60 years or older identified in this interim cohort.

Of the eight patients reported to be male, the median age was 58 years (IQR 53–58 years) and ranged between 33 and 73 years of age. For two male patients, the GP had specified HSDD as the indication. In the remaining males, the indications were 'low libido and erectile dysfunction' (two patients), 'fatigue state', 'low testosterone', 'impotence', 'orchidectomy' and 'hypopituitarism'. Although green forms were sent to GPs specifically for patients prescribed Intrinsa®, there remains a possibility that these male patients were using another testosterone patch product, since these indications relate to reduced testosterone levels. Andropatch®, marketed by GlaxoSmithKline, is a possible product that may have been used instead of Intrinsa®, since it is indicated for males rather than females.[16]

Indication

The most commonly reported primary indication was the licensed indication of HSDD in 580 patients (76.7%). There were 94 patients (12.4%) for whom an indication other than 'libido decreased' was specified; these were mainly related to hormonal problems or tiredness/lethargy. No indication was specified for 43 patients (5.7%).

Menopausal Status

In response to the question regarding the patients' menopausal status prior to starting Intrinsa®, 364 patients (48.1%) were classified as hysterectomized and bilaterally oophorectomized, 82 patients (10.9%) were hysterectomized or bilaterally oophorectomized, 127 patients (16.8%) were naturally menopausal and 45 patients (6%) were premenopausal. For the remaining 138 patients (18.2%) the menopausal status was either conflicting (where the GP provided conflicting information) or unspecified. The prescribing information states using the product in naturally menopausal women is not recommended, yet 127 patients (16.8%) were reported to be naturally menopausal.[1]

Concomitant Oestrogen Therapy

Intrinsa® must be used in combination with oestrogen, and GPs were asked to specify if a concomitant oestrogen-containing product was being used. For 493 patients (65.2%), the GP specified that the patient had been using concomitant oestrogen therapy, but in 222 patients (29.4%) the GP specified that the patient was not using concomitant oestrogen therapy. There were 42 patients (5.6%) who had used a concomitant conjugated oestrogen product; however, the use of these products with Intrinsa® is not recommended because of a lack of efficacy in clinical trials. Two of these patients were subsequently switched to estradiol-containing products.

Subgroup Analysis

The cohort was stratified based on the menopausal status of the patients (table III). A comparison was made between hysterectomized and bilaterally oophorectomized patients and naturally menopausal patients. Naturally menopausal patients were, on average, older (t-test $p < 0.001$) and were also significantly less likely to be using concomitant oestrogen (chi-squared $p < 0.001$). When premenopausal patients were compared with both hysterectomized and bilaterally oophorectomized and naturally menopausal patients they were found to be younger (t-test $p < 0.001$) and less likely to be using concomitant oestrogen therapy (chi-squared $p < 0.001$). No differences were found between the two subgroups with regard to comparisons of the proportions of

Table III. Stratification of characteristics based on status of patients

Patient status (n)[a]	Age (median [IQR])	Age range [mean (SD)]	Proportion with HSDD [n (%)]	Proportion stopped[b] [n (%)]	Proportion receiving concomitant oestrogen[c] [n (%)]
Hysterectomy/oophorectomy					
Hysterectomized and bilaterally oophorectomized (364)	49 (44–54)	27–69 [49 (7.4)]	278 (76.4)	215 (59.1)	292 (80.2)
Hysterectomized only (64)	53.5 (49–58)	38–71 [53 (7.8)]	49 (76.6)	35 (54.7)	46 (71.9)
Bilaterally oophorectomized only (18)	47 (39–54)	28–63 [46 (9.8)]	9 (50.0)	6 (33.3)	13 (72.2)
Pre-menopausal/naturally menopausal					
Naturally menopausal (127)	54 (50–58)	25–69 [53 (7.3)]	102 (80.3)	71 (55.9)	76 (59.8)
Pre-menopausal (45)[a]	43 (39–47)	28–57 [43 (6.7)]	40 (88.9)	29 (64.4)	11 (24.4)

a All patients were stated to be female except for two of the pre-menopausal patients, for whom sex was not stated.

b Did the patient stop therapy? GP ticked 'yes' and/or a reason for stopping was specified on questionnaire.

c Was patient prescribed concomitant oestrogen? GP ticked 'yes' and/or oestrogen product was specified on questionnaire.

GP = general practitioner; **HSDD** = hypoactive sexual desire disorder; **IQR** = interquartile range.

patients with HSDD or those who had stopped treatment.

The cohort was further examined to determine the number of patients who met the prescribing guidelines. Only 219 patients (29.0%) who met all of these conditions were identified. However, it must be noted that not all GPs provided a response to all of the questions, and this does not take into account the use of conjugated equine oestrogens.

Effectiveness and Duration of Treatment

In response to the specific question about stopping the drug, just over one-half of the patients (405 [53.6%]) were reported to have stopped treatment with the testosterone patch. The most frequently reported reason for stopping was 'not effective', which was reported for 17.1% of the cohort. The green form questionnaire also asks GPs to provide an opinion about the effectiveness of treatment (this is a subjective measure), and 440 GPs (58.2%) specified a response to this question: 278 (63.2%) reported that the drug was effective, and 162 (36.8%) reported that it was not effective.

After 6 months, 80 (16.8%) of the 477 patients for whom it was recorded that treatment was continuing (or for whom the date of stopping medication was given) were still being prescribed Intrinsa®; 397 (83.2%) of these patients had stopped treatment. Data on when the patient stopped Intrinsa® were not available in 279 cases (36.9% of the cohort). The most commonly reported clinical reasons for stopping were allergy (2.0%), hirsutism (1.2%) and pruritis (1.2%), which were consistent with the safety profile of the product.[1]

Discussion

The information available when a drug is launched can be limited, and postmarketing surveillance provides important information on the use of products outside the constraints of clinical trials, including use in populations that may not have been studied.[10,12] Given the indication and prescribing guidelines for Intrinsa®, there was a specific interest in examining the characteristics of the patients prescribed the drug, since the therapeutic indication details specific patient characteristics in addition to the prescribing indication. Examining the characteristics of patients is important to establish if any patients could be at potential risk from using a product outside the manufacturer's recommendation and whether prescribing guidelines are being adhered to.

In terms of general drug safety, there can be cases where a drug is prescribed outside of the terms of the approved marketing authorization, for an alternative indication or alternative patient

characteristics. This may conflict with the warnings and precautions for use of a drug, resulting in a potential risk to the patient. There could be cases where a drug is not recommended for use in certain populations but the drug has been prescribed to a patient within this population, or a drug could be prescribed to a patient for a different indication to the licensed indication. Both of these could result in potential risk to the patient, because of a lack of safety data from clinical trials. The PEM study for Intrinsa® provides real-life data for the prescribing of this product in general practice.

In the Intrinsa® study, the age range of the patient population was similar to that of the populations studied in the clinical trial phase,[2-7] and the product was being used almost exclusively in females. Intrinsa® is currently only licensed in patients with HSDD who are bilaterally oophorectomized and hysterectomized and taking concomitant oestrogen therapy. However, this PEM analysis shows that Intrinsa® is being used in general practice in naturally menopausal women and in patients not using concomitant oestrogen therapy, as well as in premenopausal women, which is important in respect to drug safety.

Naturally menopausal women using Intrinsa® could be at risk from long-term use, since safety in this population has not been established.[1] A particular potential risk from long-term use in this patient population is endometrial cancer, as the effect of testosterone on the endometrium is unknown.[1] In rodent studies, high doses of testosterone have been shown to produce endometrial tumours.[2] The proposed mechanism of action of testosterone on endometrial cells is the conversion of androgens into oestrogens in local tissues by the aromatase enzyme complex, which is responsible for stimulating the endometrium.[17] The stimulation of endometrial cell proliferation increases the probability of occurrence of mutations.[18] Aromatase activity has been found in endometrial cancer cells previously,[17,18] although no correlation between testosterone and the development of tumours has been shown.[17] The SPC states that neither conclusions nor reassurances on the incidence of endometrial cancer can be formed from current available data, so naturally menopausal women are listed under special warnings and precautions for use.[1]

Premenopausal women could also be at risk if they become pregnant whilst using Intrinsa®, since the manufacturer does not recommend its use in pregnant women or women who may become pregnant.[1] In premenopausal women who become pregnant, testosterone may induce virilizing effects on the female fetus, whilst animal studies have shown reproductive toxicity from testosterone use.[1] All potential risks from using Intrinsa® outside the therapeutic indication require further study, which can be contributed to by the continuing PEM study.

A specific safety concern relating to long-term testosterone use is that the effect on breast cancer risk is unknown.[1] Data from rodent studies has shown that high doses of testosterone can produce tumours in the mammary gland.[2] Studies have suggested that oestrogen plus progesterone increases the risk of breast cancer,[19,20] but there is conflicting data as to whether testosterone has an effect on breast cancer risk. Some studies have suggested that testosterone has a protective effect against breast cancer, whilst others have suggested that testosterone may increase breast cancer risk.[17,21,22] A recent placebo-controlled trial of postmenopausal women using a transdermal testosterone patch with no concomitant oestrogen therapy reported four women who were diagnosed with breast cancer after receiving testosterone, compared with no cases of breast cancer in the placebo group. A causal relationship could not be determined but also could not be ruled out.[8] The theoretical mechanism of action is the conversion of androgens to oestrogen by the aromatase enzyme complex present in breast tissue, or by direct stimulation of the androgen receptor found in the breast.[17] The SPC acknowledges this unknown risk and recommends that since the long-term effect of testosterone treatment on the breast is unknown, patients should be carefully monitored with regard to breast cancer.[1]

A limitation of this PEM analysis is that not all green forms that were sent to GPs have been

returned, which may introduce a non-response bias. Additionally, this study is limited to general practice and does not include patients prescribed the medicine in hospital unless treatment was continued by their GP.[12] Nevertheless, this analysis provides important information about the use of Intrinsa® in general practice and shows that in some instances the specific prescribing guidelines for using the product are not being adhered to.

Conclusion

This interim utilization analysis has provided data on 756 patients included in the PEM cohort to date. The study has highlighted that some GPs are prescribing this product outside the recommended terms of the licence, prescribing to patients who are not hysterectomized and bilaterally oophorectomized and receiving concomitant oestrogen therapy, or to those patients who do not have HSDD. Additionally, patients who are naturally menopausal or premenopausal are being prescribed Intrinsa®. Most importantly, this analysis has highlighted that only 219 patients (29.0%) in the cohort were being prescribed Intrinsa® according to the manufacturer's recommendations for the product. Since there is a lack of safety data for prescribing outside these guidelines, off-label use and use in patients where warnings or precautions may apply will continue to be monitored during the PEM study and the findings will be used to support the RMP. All events experienced by these patients will be analysed to detect any possible adverse events associated with the use of Intrinsa® outside of the licensed therapeutic indication.

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