Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Intrarosa

Active ingredient/s: Prasterone

Sponsor: Theramex Australia Pty Ltd

September 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC_{0-24}	Area under concentration time curve from time zero to 24 hours
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
COR-B	Comparable Oversea Regulator – B
DHEA	Dehydroepiandrosterone
DLP	Data lock point
EMA	European Medicines Agency
EU	European Union
HRT	Hormone replacement therapy
ITT	Intent to treat
MBS	Most bothersome symptoms
mITT	Modified intent to treat
PI	Product Information
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PT	Preferred Term
RMP	Risk management plan
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
USA	United States (of America)
VVA	Vulvar and vaginal atrophy

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Intrarosa
Active ingredient:	Prasterone
Decision:	Approved
Date of decision:	15 June 2023
Date of entry onto ARTG:	16 June 2023
ARTG number:	391550
▼*Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Theramex Australia Pty Ltd Level 22, 60 Margaret Street, Sydney NSW 2000
Dose form:	Pessary
Strength:	6.5 mg
Container:	Blister pack
Pack size:	28
Approved therapeutic use for the current submission:	*Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms*.
Route of administration:	Intravaginally
Dosage:	Intrarosa is administered intravaginally with the use of the provided applicator or with fingers. One pessary is administered once a day at bedtime. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA

does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Theramex Australia Pty Ltd (the sponsor) to register Intrarosa (prasterone) 6.5 mg, pessary, blister pack for the following proposed indication:[1]

The treatment of postmenopausal vulvovaginal atrophy.

Condition

Vulvar and vaginal atrophy (VVA) is a condition associated with loss of vaginal elasticity, dryness, decreased lubrication with irritation, dyspareunia and urinary symptoms. It is typically a consequence of reduced oestrogen levels in the affected tissues. It may symptomatically affect approximately 50% of postmenopausal women.

Current treatment options

Intravaginal oestrogen therapies are the most effective treatment for symptoms of VVA (for example, vaginal dryness, dyspareunia, urinary frequency, dysuria, nocturia and urgency). Although less effective, non-hormonal therapies (vaginal moisturisers or lubricants) can be used if vaginal dryness is the only symptom.

This submission was submitted through the TGA's Comparable Overseas Regulator B (COR-B) process, using evaluation reports from European Medicines Agency (EMA). The full dossier was submitted to the TGA.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes. This is a new chemical entity application to register Intrarosa (prasterone) 6.5 mg pessary via the COR-B pathway.

The European Union (EU) approved Intrarosa via the Centralised Procedure on 8 January 2018 for the indication:

Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

For Australia, the sponsor has proposed the following indication for Australia:

Intrarosa is indicated for the treatment of postmenopausal vulvovaginal atrophy.

The broader nature of the indication proposed for Australia should have been rejected (or converted to a different pathway) at submission assessment stage by the submission assessment evaluator. This has been rectified during the evaluation process instead, through the clinical evaluator and decision Delegate.

At the time the TGA considered this submission, a similar submission had been approved in United States of America (USA) on 16 November 2016, European Union on 8 January 2018,

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

United Kingdom on 4 March 2022, Canada on 1 November 2019 and Switzerland on 19 May 2020.

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	16 October 2015	Approved on 16 November 2016	*Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.*
European Union	17 December 2015	Approved on 8 January 2018	*Treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms*
United Kingdom	22 December 2021	Approved on 4 March 2022	*Treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms*
Canada	29 September 2016	Approved on 1 November 2019	*Treatment of postmenopausal vulvovaginal atrophy*
Switzerland	1 November 2018	Approved on 19 May 2020	*Local treatment of vulvovaginal atrophy in postmenopausal women.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2022-02509-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2022
First round evaluation completed	18 January 2023
Sponsor provides responses on questions raised in first round evaluation	17 March 2023

Description	Date
Second round evaluation completed	28 March 2023
Delegate's Overall benefit-risk assessment	13 June 2023
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	15 June 2023
Administrative activities and registration on the ARTG completed	16 June 2023
Number of working days from submission dossier acceptance to registration decision*	150

* The COR-B process has a 175 working day evaluation and decision timeframe.

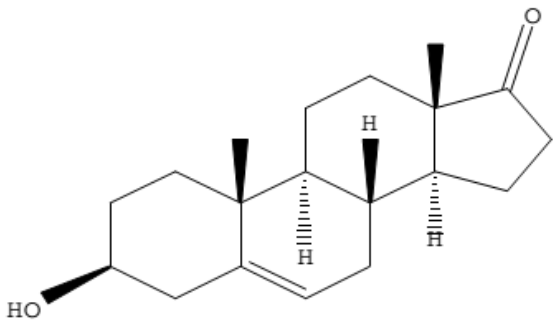
Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Prasterone (3β-hydroxyandrost-5-en-17-one, see Figure 1) or dehydroepiandrosterone (DHEA), is a precursor steroid which is inactive by itself, with no estrogenic, androgenic, or other hormonal activity. Following intravaginal administration, prasterone is transformed inside the vaginal cells into estrogens and androgens.

Figure 1: Chemical structure of prasterone



The drug product is administered intravaginally with the use of a provided applicator or with fingers once a day at bedtime (6.5 mg daily dose) and is indicated for the treatment of postmenopausal vulvovaginal atrophy.

The drug product is a white, bullet-shaped pessary, approximately 28 mm long and 8.6 mm in diameter at its widest end and packaged as a kit with 28 pessaries in blister packs and six

applicators. The applicators are intended to be reused with rinsing under running water and discarded after a one week of usage. Two additional applicators are provided if necessary.

Approval is recommended for registration of the proposed product from a pharmaceutical chemistry perspective.

Nonclinical

The nonclinical dossier contained a limited set of studies (on pharmacokinetic drug interactions, repeat-dose toxicity and genotoxicity) plus a large number of published papers (but was not a formal literature based-submission with an approved systematic search strategy). The nonclinical dossier was of poor overall quality.

Prasterone is the synthetic equivalent of DHEA, an endogenous steroid precursor of androgens and estrogens. Intrarosa is intended as a pro-drug providing local hormone replacement therapy. Conversion to hormone metabolites is cell specific.

Supporting utility for the proposed indication, vaginal (and percutaneous) administration of prasterone was shown to prevent the decreased weight and histological signs of vaginal atrophy induced by ovariectomy in rats. Steroidogenic enzyme and sex hormone receptor expression in the monkey vagina was described.

Besides effects mediated by the androgens and estrogens formed by prasterone, some direct effects on receptors and ion channels are reported for the compound in the literature. Such secondary activity and limited information available on safety pharmacology do not raise concerns relevant to patients given limited/physiological systemic exposure.

Rapid absorption after intravaginal administration was demonstrated in ovariectomised rats. Systemic exposure to prasterone and hormone metabolites after intravaginal administration was apparent in rats (and humans).

Prasterone was shown not to inhibit CYP1A2, 2B7, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4;[2] at clinically relevant concentrations *in vitro*. Transporter inhibition and CYP induction potential were not investigated. Based on the available data and considering the extent of systemic exposure, pharmacokinetic drug interactions mediated by prasterone are not expected in patients.

Repeat-dose toxicity studies were performed in rats (six months duration) and cynomolgus monkeys (12 months). These were not designed as recommended in the relevant TGA-adopted EMA guideline, involving oral administration rather than using the clinical route and employing too few dose groups to appropriately characterise dose-response relationships. While not ideal, oral administration has allowed for higher systemic exposure to be achieved than would be obtained with intravaginal administration.

Prasterone was well tolerated in the two species at doses providing moderate to high multiples of the systemic exposure in patients. Findings in treated animals were attributable to the

[2] Cytochrome P450 (CYP) enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

pharmacology of prasterone (estrogenic/androgenic effects). Female rats showed microscopic changes in the uterus and vagina. No treatment-related histopathological changes were observed with prasterone in monkeys, although ovary, uterus and vagina weight were altered.

Compensating for the absence of a repeat-dose toxicity study by the intravaginal route, the clinical program included examination of cervical cytology and endometrial biopsy.

Prasterone was negative in the standard battery of tests for genotoxicity.

Carcinogenicity studies were not performed, which is considered to be acceptable given the drug's status as an endogenous compound with a low level of systemic exposure, that data show that systemic sex hormone levels in prasterone-treated postmenopausal women are essentially the same as in women receiving a placebo, and given existing knowledge for androgens and estrogens. These have been demonstrated to be carcinogenic in animals, which raises concern for potential local carcinogenic effects (including to the cervix and endometrium).

No reproductive and developmental toxicity studies were included in the submission, which is acceptable given the patient population (exclusively postmenopausal women). Pregnancy Category D,[3] as proposed by the sponsor, is appropriate. The product should also be contraindicated in pregnancy, however, consistent with similar hormonal products.

Conclusions and recommendations

There are no nonclinical objections to the registration of Intrarosa for the proposed indication.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- One Phase I/II study, Study ERC-213
- Five Phase III studies, Studies ERC-210, ERC-231, ERC-238, ERC-234 and ERC-230 (see Table 3)

[3] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Table 3: Overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report; Papers Based on Study Data
PK (phase I/II)	ERC-213 NCT00429806	5.3.3.2/ ERC-213	Evaluation of the systemic bioavailability of DHEA and its metabolites and the pharmacokinetics of vaginal ovules at four different DHEA concentrations.	Randomized, double-blind, placebo-controlled	0%, 0.50%, 1.0% and 1.8% DHEA vaginal ovules; once daily	40	Postmenopausal women with vaginal atrophy	7 days	Completed; Full Report; Papers: Labrie, Cusan et al. 2008a Labrie, Cusan et al. 2008b Labrie, Martel et al. 2013 Labrie and Martel, 2017
Efficacy /Safety (phase III)	ERC-210 NCT01846442	5.3.5.1/ ERC-210	To determine the dose-response of vaginal mucosa parameters to the local action of DHEA	Randomized, double-blind, placebo-controlled	0%, 0.25%, 0.50% and 1.0% DHEA vaginal ovules; once daily	218	Postmenopausal women with vaginal atrophy	12 weeks	Completed; Full Report; Papers: Labrie, Archer et al. 2009a Labrie, Archer et al. 2009b Labrie, Archer et al. 2009c Labrie, Archer et al. 2010 Labrie 2010 Labrie, Archer et al. 2011 Labrie, Archer et al. 2014 Portman, Labrie et al. 2015 Martel, Labrie et al. 2016 Archer, Labrie et al. 2017 Labrie, Archer et al. 2017
Efficacy /Safety (phase III) PIVOTAL	ERC-231 NCT01256684	5.3.5.1/ ERC-231	To confirm the efficacy of intravaginal DHEA on the symptoms and signs of vaginal atrophy	Randomized, double-blind, placebo-controlled	0%, 0.25% and 0.50% DHEA vaginal ovules; once daily	255	Postmenopausal women with vaginal atrophy; Dyspareunia as most bothersome symptom	12 weeks	Completed; Full Report; Papers: Archer, Labrie et al. 2015 Portman, Labrie et al. 2015 Martel, Labrie et al. 2016 Archer, Labrie et al. 2017 Labrie, Archer et al. 2017
Efficacy /Safety (phase III) PIVOTAL	ERC-238 NCT02013544	5.3.5.1/ ERC-238	To confirm the efficacy of intravaginal DHEA on moderate to severe (MS) pain at sexual activity (dyspareunia) as most bothersome symptom (MBS) of vulvovaginal atrophy due to menopause and to collect further data on subjects exposed to intravaginal DHEA	Randomized, double-blind, placebo-controlled (2:1 ratio between DHEA:placebo)	0.0% or 0.50% DHEA vaginal ovules; once daily	558	Postmenopausal women with vaginal atrophy; Dyspareunia as most bothersome symptom	12 weeks	Completed; Full Report; Papers: Labrie, DeRogatis et al. 2015 Ke, Labrie et al. 2015 Labrie, Montesino et al. 2015 Labrie, Archer et al. 2016 Montesino, Labrie et al. 2016 Martel, Labrie et al. 2016 Archer, Labrie et al. 2017 Labrie, Archer et al. 2017
Efficacy /Safety (phase III)	ERC-234 NCT01358760	5.3.5.1/ ERC-234	To confirm the efficacy of intravaginal DHEA on vaginal dryness, a symptom of vaginal atrophy, in postmenopausal women suffering from vaginal dryness	Randomized, double-blind, placebo-controlled	0, 0.25% and 0.5% DHEA vaginal ovules; once daily for 2 weeks followed by twice weekly for 10 weeks	450	Postmenopausal women with vaginal atrophy; Dryness as most bothersome symptom	12 weeks	Completed; Full Report; Papers: Bouchard, Labrie et al. 2015 Portman, Labrie et al. 2015
Safety (phase III)	ERC-230 NCT01256671	5.3.5.2/ ERC-230	To assess the long term safety of intravaginal DHEA	Open-label	0.50% DHEA vaginal ovules; once daily	530	Postmenopausal women having self-identified at least one mild to severe vaginal atrophy symptom	52 weeks	Completed; Full Report; Papers: Labrie, Archer et al. 2015 Ke, Gonthier et al. 2015 Portman, Labrie et al. 2015 Bouchard, Labrie et al. 2016 Martel, Labrie et al. 2016 Archer, Labrie et al. 2017

Pharmacology

Pharmacokinetics (PK) data were provided in Study ERC-213, a Phase I, randomised, double blind, placebo-controlled study to evaluate the systemic bioavailability of DHEA and its metabolites following daily intravaginal administration of DHEA at three different strengths for seven days in postmenopausal women with VVA.

The study enrolled 40 postmenopausal women, randomised to 1 of 4 groups (n = 10 per group); DHEA 0%, 0.5% (6.5 mg – proposed strength for registration), 1% (13 mg) or 1.8% (23.4 mg). One pessary was administered once daily in the evening with a single use applicator. Blood sampling for PK analysis was collected at screening and at specified time points after dosing on

Day 1 and Day 7. The study was conducted at a single centre in Canada in 2006. The methodology and results are presented in sponsor submitted dossier.

Compared to placebo, the area under concentration time curve from time zero to 24 hours (AUC_{0-24}) of DHEA increased:

- 2.68-fold, 3.06-fold and 5.05-fold for the 0.5%, 1% and 1.8% strengths, respectively (Day 1).
- 2.26-fold, 3.07-fold and 4.61-fold for the 0.5%, 1% and 1.8% strengths, respectively (Day 7).

Pharmacokinetics

Absorption

In Study ERC-213, administration of the Intrarosa pessary once daily for seven days resulted in a mean prasterone maximum concentration (C_{max}) and AUC_{0-24} at Day 7 of 4.4 ng/mL and 56.2 ng h/mL, respectively. The C_{max} and AUC_{0-24} of the metabolites testosterone and oestradiol were also slightly higher compared to placebo, but all remained within normal values of postmenopausal women (< 10 pg oestradiol/mL; < 0.26 ng testosterone/mL) as measured by validated mass spectrometry-based assays for both the study samples and reference values.

Distribution

The distribution of intravaginal (exogenous) prasterone is mainly local but some increase in systemic exposure is observed especially for the metabolites but within normal values.

Metabolism

Exogenous prasterone is metabolised in the same manner as endogenous prasterone. Systemic metabolism has not been studied in this application.

Excretion and elimination

Systemic excretion has not been studied specifically for this application.

Pharmacodynamics

Mechanism of action

Prasterone is biochemically and biologically identical to endogenous human DHEA, a precursor steroid with no or little pharmacological activity itself that is converted into oestrogens and androgens. These metabolites formed from prasterone activate oestrogen and androgen receptors.

Prasterone administered locally in the vagina enters the vaginal cells and is converted intracellularly into oestrogens and androgens, depending upon the level of particular steroidogenic enzymes expressed in each cell type.

An increase in the number of superficial and intermediate cells and decrease in the number of parabasal cells in the vaginal mucosa is noted. In addition, the vaginal pH decreased towards the normal range, thus facilitating the growth of the normal bacterial flora.

Primary pharmacology

There were no specific Phase I or II studies to investigate the primary pharmacology of DHEA. The mechanism of action of DHEA administered intravaginally is not fully elucidated.

In the Phase I Study ERC-213 described in section above, vaginal maturation index and vaginal pH were assessed pre-treatment (Day 1) and after 7 days of treatment to assess the effect of DHEA and placebo pessaries on the vaginal mucosa:

- At Day 7, there was a significant increase in vaginal maturation index of 107%, 75% and 150% in the DHEA 0.5%, 1% and 1.8% groups, respectively, versus no change in the placebo group.
- At Day 7, there was a significant decrease in vaginal pH in all DHEA groups and no change in vaginal pH in the placebo group.

The overseas evaluator report includes a summary of findings from the Phase III studies relevant to pharmacodynamics , namely changes in percentages of superficial and parabasal cells. These parameters were efficacy endpoints in the pivotal studies.

Efficacy

An overview of all studies is listed in Table 3.

The efficacy and safety of Intrarosa is mainly assessed from data from two pivotal Phase III studies (Studies ERC-231 and ERC-238). They were randomised, double blind, and placebo-controlled to assess the efficacy of 6.5 mg of vaginal prasterone in postmenopausal women with VVA. Prasterone was administered vaginally once a day for 12 weeks. There were four co-primary endpoints including change in vaginal maturation index (increase in % of superficial cells, decrease in % of parabasal cells), change in vaginal pH and improvement in dyspareunia.

Additional supportive data are also provided from an open label safety study (Study ERC-230) which was conducted for 52 weeks to assess the safety outcome of long-term administration.

No active comparator group was included in the clinical program.

Additional Phase III efficacy and safety studies (Study ERC-234 and Study ERC-210) included an administration regimen different to the proposed regimen and a dose-ranging study, respectively and can therefore be considered supportive only.

Study ERC-231 (pivotal Phase III trial)

Study ERC-231 is a 12-week, Phase III, randomised, double blind, placebo-controlled, multicentre, three arm, parallel group study to confirm the efficacy of daily intravaginal administration of DHEA compared to placebo on the symptoms and signs of vaginal atrophy in postmenopausal women suffering from moderate to severe dyspareunia as most bothersome symptoms (MBS) of VVA at Baseline. The study was conducted at 33 sites in Canada and the USA from 30 November 2010 to 29 July 2011.

Eligible subjects were postmenopausal women 40 to 75 years of age who self-identified moderate to severe dyspareunia as the MBS (that is symptom severity score of 2 or 3), with vaginal pH > 5 and ≤ 5% superficial cells on vaginal smear at Baseline. A full list of inclusion/exclusion criteria is listed in sponsor submitted dossier.

Following six-week screening period, 255 participants were randomised in 1:1:1 ratio to 1 of 3 treatment arms; placebo (n = 82), 0.25% DHEA (n = 87) and 0.50% DHEA (n = 87 Intrarosa). All participants administered 1 pessary before bedtime for 12 weeks.

The four co-primary endpoints were changes in percentage of parabasal cells and superficial cells, vaginal pH and dyspareunia severity score. Vaginal smears were obtained from the middle or second third of the side wall of the vagina and sent to central laboratory for determination of vaginal cell maturation index by a blinded experienced cytopathologist. For the vaginal cell

maturation evaluation, a 100-cell count was performed to classify cells as parabasal (including basal), intermediate, and superficial squamous cell types. Vaginal pH was measured with pH indicator strip applied to the lateral wall of the vagina. Dyspareunia was self-assessed via a questionnaire using a 4-point severity score (none [0], mild [1], moderate [2], severe [3]).

Baseline demographics and characteristics were similar in each group. The majority of subjects were White (86 to 95%), with mean age 58.55 years and mean body mass index 26.08 kg/m^2. There were 58% subjects with previous hormone replacement therapy (HRT) use, 61% with hysterectomy and 33% with (any) ovariectomy (25% bilateral).

Magnitude of the treatment effect and its clinical significance

Results for the co-primary endpoints for 0.5% DHEA (Intrarosa) and placebo are summarised in Table 4.

Table 4: Studies ERC-210, ERC-231 and ERC-238. Summary of co-primary efficacy endpoints (intent-to-treat population)

	ERC-210[1] Daily for 12 Weeks		ERC-231 Daily for 12 Weeks		ERC-238 Daily for 12 Weeks	
Dose of Prasterone	**0.50%**	**Placebo**	**0.50%**	**Placebo**	**0.50%**	**Placebo**
Superficial Cells (%) n =	**30**	26	**81**	77	**325**	157
Baseline	**0.40**	0.62	**0.68**	0.73	**1.02**	1.04
Week 12	**5.20**	0.54	**6.30**	1.64	**11.22**	2.78
Mean change from baseline	**4.80**	-0.08	**5.62**	0.91	**10.20**	1.75
Difference from placebo	**4.88**	-	**4.71**	-	**8.46**	-
p-values vs placebo[2]	**0.0111**	-	**<0.0001**	-	**<0.0001**	-
Parabasal Cells (%) n =	**30**	26	**81**	77	**325**	157
Baseline	**53.40**	46.73	**65.05**	68.48	**54.25**	51.66
Week 12	**11.00**	47.81	**17.65**	66.86	**12.74**	39.68
Mean change from baseline	**-42.40**	1.08	**-47.40**	-1.62	**-41.51**	-11.98
Difference from placebo	**-43.48**	-	**-45.77**	-	**-29.53**	-
p-values vs placebo[2]	**<0.0001**	-	**<0.0001**	-	**<0.0001**	-
pH (units) n=	**30**	26	**81**	77	**325**	157
Baseline	**6.64**	6.49	**6.47**	6.51	**6.34**	6.32
Week 12	**5.17**	6.01	**5.43**	6.31	**5.39**	6.05
Mean change from baseline	**-1.47**	-0.48	**-1.04**	-0.21	**-0.94**	-0.27
Difference from placebo	**-0.99**	-	**-0.83**	-	**-0.67**	-
p-values vs placebo[2]	**0.0001**	-	**<0.0001**	-	**<0.0001**	-
Dyspareunia n =	**30**	26	**81**	77	**325**	157
Baseline	**2.73**	2.77	**2.63**	2.58	**2.54**	2.56
Week 12	**1.10**	2.35	**1.36**	1.71	**1.13**	1.50
Mean change from baseline	**-1.63**	-0.42	**-1.27**	-0.87	**-1.42**	-1.06
Difference from placebo	**-1.21**	-	**-0.40**	-	**-0.35**	-
p-values vs placebo[2]	**<0.0001**	-	**0.0132**	-	**0.0002**	-

[1]: Results from a post-hoc analysis that takes into account the adjustment for multiplicity in the choice of dyspareunia among the 3 most bothersome symptoms of ERC-210. Applying the Bonferroni correction, the p-value for statistical significance for each of the 4 co-primary endpoints was assessed against 0.05/3 = 0.0167.

[2]: ANCOVA test with treatment group as the main factor and baseline value as the covariate.

Study ERC-238 (pivotal Phase III trial)

Study ERC-238 is 12-week, Phase III, randomised, double blind, placebo-controlled, multicentre, two arm, parallel group study to confirm the efficacy of intravaginal 0.50% DHEA versus placebo on moderate to severe dyspareunia as the MBS of VVA in postmenopausal women. The study was conducted at 38 sites in Canada and the USA from 11 February 2014 to 6 January 2015.

Postmenopausal women aged 40 to 80 years with less than or equal to 5% superficial cells on vaginal smear, vaginal pH greater than 5, who self-identified moderate to severe dyspareunia as

their MBS of VVA were eligible to participate. Inclusion/exclusion criteria are mostly comparable with Study ERC-231.

Eligible subjects were randomised in 2:1 ratio to 0.5% DHEA (n = 376; Intrarosa) or placebo (n = 182) and administered one pessary each evening for 12 weeks.

The four co-primary endpoints were as per Study ERC-231. Efficacy analyses were conducted on the intent-to-treat (ITT) population (n = 482; n = 325 DHEA 0.50%, n = 157 placebo), as previously defined, with the 12-week assessment the primary time point for analysis.

Statistical methods were consistent with those described for Study ERC-231. For the co-primary endpoint dyspareunia, an additional analysis was conducted on a modified ITT population (mITT) comprising women from the ITT population who had post-baseline sexual activity at least once before evaluation of dyspareunia at Week 6, Week 12 or discontinuation (n = 448; n = 305 DHEA 0.50%, n = 143 placebo).

Baseline demographics and characteristics of subjects in the two treatment groups were similar. Study subjects were predominately White (90%), with mean age 59.5 years and mean body mass index of 26.4 kg/m^2. The proportion of subjects with previous HRT use, hysterectomy and ovariectomy (any) was 42%, 38% and 26% respectively.

Magnitude of the treatment effect and its clinical significance

Results for the co-primary endpoints are summarised above in Table 4. Analysis of the co-primary endpoint dyspareunia in the mITT population was similar to ITT population with an improvement of 0.34 severity score unit over placebo (p = 0.0003).

In the placebo group, greater mean changes from Baseline were observed for each of the four co-primary endpoints in Study ERC-238 than in Study ERC-231. The sponsor did not have a '*well-supported explanation*' for the observed study difference, however noted a certain level of sexual activity was required in Study ERC-238, which may have beneficial effects on vaginal physiology and could partially explain the greater placebo effect. The overseas evaluator considered the explanation plausible, but difficult to confirm as data relating to frequency of sexual intercourse was not collected in either pivotal study. The issue was considered resolved.

Study ERC-210 (supportive study)

Study ERC-210 is a 12-week, Phase III, randomised, double blind, placebo-controlled dose response study comparing the effect of different doses of DHEA pessaries on vaginal mucosa parameters in postmenopausal women with vaginal atrophy. The study was conducted at eight centres in Canada and USA from 28 June 2007 to 23 May 2008.

Postmenopausal women aged 40 to 75 years with low maturation index, vaginal pH greater than 5 and at least one self-identified moderate-severe symptom of vaginal atrophy (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal pain associated with sexual activity) were eligible to participate. Inclusion/exclusion criteria are listed in sponsor submitted dossier.

There were 218 participants randomised equally to one of four treatment arms (n = 54 to 56 each arm): 0.0% DHEA (placebo), 0.25% (3.25 mg) DHEA, 0.5% (6.5 mg; Intrarosa) DHEA or 1.0% (13 mg) DHEA. All participants administered one pessary daily in the evening for 12 weeks.

The mean (standard deviation) age of participants in the ITT population (n = 216) was 58 (5.5) years.

Magnitude of the treatment effect and its clinical significance

Results for the four co-primary endpoints after 12 weeks of treatment (ITT population) for 0.50% DHEA (Intrarosa) and placebo are summarised in Table 4.

For all three DHEA groups at Week 12, there was a significant decrease from Baseline in the percentage of parabasal cells, significant increase from Baseline in the percentage of superficial cells and significant decrease in vaginal pH.

Safety

Exposure

Safety data were generated from six clinical studies (Table 3). 1196 postmenopausal women were treated with prasterone 6.5 mg (Intrarosa) during the clinical trial program, including 435 receiving treatment for 52 weeks. The extent of exposure in those studies is shown in Table 5. Additionally, post-market data are available.

Table 5: Exposure to intravaginal dehydroepiandrosterone (safety population)

Duration of treatment	0.25% DHEA (3.25 mg) N=282 N (%)	0.50% DHEA (6.5 mg) N=1196 N (%)	1.0% DHEA (13 mg) N=64 N (%)	1.8% DHEA (23.4 mg) N=10 N (%)	Overall N=1552 N (%)
At least one day of treatment	282 (100)	1196 (100)	64 (100)	10 (100)	1552 (100)
At least 10 weeks of treatment	251 (89.0)	1116 (93.3)	51 (79.7)	0	1418 (91.4)
At least 24 weeks of treatment	0	468 (39.1)	0	0	468 (30.2)
At least 50 weeks of treatment	0	435 (36.4)	0	0	435 (28.0)

Adverse event overview is listed in Table 6.

Table 6: Overview of treatment-emergent adverse events to Week 16 (safety population)

Parameters	Placebo N=474	0.25%DHEA (3.25 mg) N=282	0.50%DHEA (6.5 mg) N=1196	1.0%DHEA (13.0 mg) N=64	Overall[1] N=1542
Number (%) of subjects					
Any TEAE[2,3]	226 (47.7)	150 (53.2)	627 (52.4)	41 (64.1)	818 (53.0)
Any possibly drug-related TEAE	36 (7.6)	14 (5.0)	82 (6.9)	4 (6.3)	100 (6.5)
Any drug-related TEAE	18 (3.8)	12 (4.3)	110 (9.2)	0	122 (7.9)
Maximum intensity (severity) for any TEAE[4]					
Missing	0	0	0	0	0
Mild	113 (23.8)	63 (22.3)	312 (26.1)	16 (25.0)	391 (25.4)
Moderate	104 (21.9)	80 (28.4)	295 (24.7)	18 (28.1)	393 (25.5)
Severe	9 (1.9)	7 (2.5)	19 (1.6)	7 (10.9)	33 (2.1)
Life-threatening	0	0	1 (0.1)	0	1 (0.1)
Maximum intensity (severity) for possibly drug-related or drug-related TEAEs[5]					
Missing	0	0	0	0	0
Mild	30 (6.3)	11 (3.9)	107 (8.9)	0	118 (7.7)
Moderate	12 (2.5)	8 (2.8)	44 (3.7)	3 (4.7)	55 (3.6)
Severe	0	1 (0)	0	0	1 (0.01)
TEAEs with outcome death	0	0	0	0	0
Any Serious TEAE[6]	5 (1.1)	5 (1.8)	16 (1.3)	0	21 (1.4)
Any possibly drug-related or drug-related Serious TEAE	0	0	1 (0.1)	0	1 (0.1)

[1] Including data of 0.25%, 0.50% and 1.0% DHEA doses from studies ERC-210, ERC-213, ERC-230 (up to Week 16), ERC-231, ERC-234 and ERC-238. Data from 10 subjects treated for 1 week with 1.8% DHEA are not included.

[2] TEAE (treatment-emergent adverse event): Any event that starts or worsens after the start of study treatment through 30 days after the last dose of study treatment.

An overview of treatment-emergent adverse events (TEAE) is shown in Table 6 (by severity and whether related to drug), Table 7 (by system organ class (SOC) and Preferred Term (PT) up to Week 16), and Table 8 (by SOC and PT up to Week 52).

Table 7: Overview of treatment-emergent adverse events by Primary System Organ Class and Preferred Term to Week 16 (Safety Population, Preferred Terms with an incidence of at least 1% in any treatment group).

Primary System Organ Class Preferred term[1]	Placebo N=474	0.25%DHEA (3.25 mg) N=282	0.50%DHEA (6.5 mg) N=1196	1.0%DHEA (13.0 mg) N=64	Overall[2] N=1542
Number (%) of subjects with at least one TEAE[3]	**226 (47.7)**	**150 (53.2)**	**627 (52.4)**	**41 (64.1)**	**818 (53.0)**
Gastrointestinal disorders	**44 (9.3)**	**30 (10.6)**	**85 (7.1)**	**11 (17.2)**	**126 (8.2)**
Abdominal pain	14 (3.0)	5 (1.8)	21 (1.8)	5 (7.8)	31 (2.0)
Diarrhoea	8 (1.7)	6 (2.1)	13 (1.1)	1 (1.6)	20 (1.3)
Nausea	14 (3.0)	5 (1.8)	19 (1.6)	4 (6.3)	28 (1.8)
General disorders and administration site complications	**31 (6.5)**	**17 (6.0)**	**131 (11.0)**	**10 (15.6)**	**158 (10.2)**
Application site discharge	16 (3.4)	11 (3.9)	99 (8.3)	0	110 (7.1)
Fatigue	6 (1.3)	3 (1.1)	7 (0.6)	6 (9.4)	16 (1.0)
Infections and infestations	**80 (16.9)**	**56 (19.9)**	**209 (17.5)**	**20 (31.3)**	**285 (18.5)**
Nasopharyngitis	22 (4.6)	16 (5.7)	40 (3.3)	5 (7.8)	61 (4.0)
Sinusitis	7 (1.5)	4 (1.4)	19 (1.6)	2 (3.1)	25 (1.6)
Urinary tract infection	21 (4.4)	18 (6.4)	57 (4.8)	2 (3.1)	77 (5.0)
Investigations	**19 (4.0)**	**10 (3.5)**	**63 (5.3)**	**0**	**73 (4.7)**
Weight increased	6 (1.3)	0	21 (1.8)	0	21 (1.4)
Musculoskeletal and connective tissue disorders	**37 (7.8)**	**30 (10.6)**	**69 (5.8)**	**11 (17.2)**	**110 (7.1)**
Arthralgia	7 (1.5)	4 (1.4)	15 (1.3)	2 (3.1)	21 (1.4)
Back pain	11 (2.3)	8 (2.8)	15 (1.3)	5 (7.8)	28 (1.8)
Pain in extremity	6 (1.3)	11 (3.9)	8 (0.7)	3 (4.7)	22 (1.4)
Nervous system disorders	**18 (3.8)**	**23 (8.2)**	**58 (4.8)**	**10 (15.6)**	**91 (5.9)**
Headache	14 (3.0)	12 (4.3)	35 (2.9)	6 (9.4)	53 (3.4)
Reproductive system and breast disorders	**59 (12.4)**	**42 (14.9)**	**155 (13.0)**	**12 (18.8)**	**209 (13.6)**
Cervical dysplasia	6 (1.3)	8 (2.8)	21 (1.8)	0	29 (1.9)
Hot flush	13 (2.7)	7 (2.5)	32 (2.7)	5 (7.8)	44 (2.9)
Vaginal discharge	6 (1.3)	9 (3.2)	19 (1.6)	2 (3.1)	30 (1.9)
Vaginal haemorrhage	6 (1.3)	4 (1.4)	14 (1.2)	0	18 (1.2)
Vulvovaginal burning sensation	8 (1.7)	1 (0.4)	16 (1.3)	4 (6.3)	21 (1.4)
Vulvovaginal pruritus	8 (1.7)	6 (2.1)	17 (1.4)	5 (7.8)	28 (1.8)

[1] Subjects were counted only once within each preferred term.
[2] Including data of 0.25%, 0.50% and 1.0% DHEA doses from studies ERC-210, ERC-213, ERC-230 (up to Week 16), ERC-231, ERC-234 and ERC-238. Data from 10 subjects treated for 1 week with 1.8% DHEA in ERC-213 are not included.
[3] TEAE (treatment-emergent adverse event): Any event that starts or worsens after the start of study treatment through 30 days after the last dose of study treatment. (AEs coded with MedDRA version 16.1.)

There were 40 (3.3%) 0.5% DHEA subjects and 10 (2.1%) placebo subjects discontinuing studies due to TEAEs, including 31 subjects from Study ERC-230. Application site discharge (0.5%) and human papilloma test positive (0.2%) were the most common TEAEs leading to discontinuation of 0.50% DHEA.

Table 8: Overview of treatment-emergent adverse events by primary System Organ Class and Preferred Term to Week 52 (Safety Population, Preferred Terms with an incidence of at least 1% in any treatment group).

Primary System Organ Class Preferred term[1]	Placebo N=474 (Days at risk: 50,546) [IR]	0.25%DHEA (3.25 mg) N=282 (Days at risk: 29,897) [IR]	0.50%DHEA (6.5 mg) N=1196 (Days at risk: 258,109) [IR]	1.0%DHEA (13.0 mg) N=64 (Days at risk: 6,254) [IR]	Overall[2] N=1542 (Days at risk: 294,260) [IR]
Number (%) of subjects with at least one TEAE[3]	**226 (47.7)**	**150 (53.2)**	**769 (64.3)**	**41 (64.1)**	**960 (62.3)**
Gastrointestinal disorders	**44 (9.3)/ [9.9]**	**30 (10.6)/ [11.4]**	**124 (10.4)/ [5.5]**	**11 (17.2)/ [20.1]**	**165 (10.7)/ [6.4]**
Abdominal pain	14 (3.0)/ [3.2]	5 (1.8)/ [1.9]	28 (2.3)/ [1.2]	5 (7.8)/ [9.1]	38 (2.5)/ [1.5]
Diarrhea	8 (1.7)/ [1.8]	6 (2.1)/ [2.3]	15 (1.3)/ [0.7]	1 (1.6)/ [1.8]	22 (1.4)/ [0.9]
Nausea	14 (3.0)/ [3.2]	5 (1.8)/ [1.9]	28 (2.3)/ [1.2]	4 (6.3)/ [7.3]	37 (2.4)/ [1.4]
General disorders and administration site complications	**31 (6.5)/ [7.0]**	**17 (6.0)/ [6.5]**	**142 (11.9)/ [6.3]**	**10 (15.6)/ [18.2]**	**169 (11.0)/ [6.5]**
Application site discharge	16 (3.4)/ [3.6]	11 (3.9)/ [4.2]	104 (8.7)/ [4.6]	0	115 (7.5)/ [4.5]
Fatigue	6 (1.3)/ [1.4]	3 (1.1)/ [1.1]	10 (0.8)/ [0.4]	6 (9.4)/ [10.9]	19 (1.2)/ [0.7]
Infections and infestations	**80 (16.9)/ [18.0]**	**56 (19.9)/ [21.4]**	**331 (27.7)/ [14.6]**	**20 (31.3)/ [36.5]**	**407 (26.4)/ [15.8]**
Bronchitis	4 (0.8)/ [0.9]	2 (0.7)/ [0.8]	18 (1.5)/ [0.8]	0	20 (1.3)/ [0.8]
Influenza	3 (0.6)/ [0.7]	3 (1.1)/ [1.1]	20 (1.7)/ [0.9]	2 (3.1)/ [3.6]	25 (1.6)/ [1.0]
Nasopharyngitis	22 (4.6)/ [5.0]	16 (5.7)/ [6.1]	73 (6.1)/ [3.2]	5 (7.8)/ [9.1]	94 (6.1)/ [3.6]
Sinusitis	7 (1.5)/ [1.6]	4 (1.4)/ [1.5]	27 (2.3)/ [1.2]	2 (3.1)/ [3.6]	33 (2.1)/ [1.3]
Upper respiratory tract infection	3 (0.6)/ [0.7]	3 (1.1)/ [1.1]	24 (2.0)/ [1.1]	0	27 (1.8)/ [1.0]
Urinary tract infection	21 (4.4)/ [4.7]	18 (6.4)/ [6.9]	91 (7.6)/ [4.0]	2 (3.1)/ [3.6]	111(7.2)/ [4.3]
Vaginitis bacterial	5 (1.1)/ [1.1]	1 (0.4)/ [0.4]	15 (1.3)/ [0.7]	1 (1.6)/ [1.8]	17 (1.1)/ [0.7]
Investigations	**19 (4.0)/ [4.3]**	**10 (3.5)/ [3.8]**	**111 (9.3)/ [4.9]**	**0**	**121 (7.8)/ [4.7]**
Weight decreased	6 (1.3)/ [1.4]	1 (0.4)/ [0.4]	31 (2.6)/ [1.4]	0	32 (2.1)/ [1.2]
Weight increased	6 (1.3)/ [1.4]	0	30 (2.5)/ [1.3]	0	30 (1.9)/ [1.2]
Musculoskeletal and connective tissue disorders	**37 (7.8)/ [8.3]**	**30 (10.6)/ [11.4]**	**110 (9.2)/ [4.9]**	**11 (17.2)/ [20.1]**	**151 (9.8)/ [5.8]**
Arthralgia	7 (1.5)/ [1.6]	4 (1.4)/ [1.5]	20 (1.7)/ [0.9]	2 (3.1)/ [3.6]	26 (1.7)/ [1.0]
Back pain	11 (2.3)/ [2.5]	8 (2.8)/ [3.1]	30 (2.5)/ [1.3]	5 (7.8)/ [9.1]	43 (2.8)/ [1.7]
Pain in extremity	6 (1.3)/ [1.4]	11 (3.9)/ [4.2]	12 (1.0)/ [0.5]	3 (4.7)/ [5.5]	26 (1.7)/ [1.0]
Nervous system disorders	**18 (3.8)/ [4.1]**	**23 (8.2)/ [8.8]**	**76 (6.4)/ [3.4]**	**10 (15.6)/ [18.2]**	**109 (7.1)/ [4.2]**
Headache	14 (3.0)/ [3.2]	12 (4.3)/ [4.6]	45 (3.8)/ [2.0]	6 (9.4)/ [10.9]	63 (4.1)/ [2.4]
Psychiatric disorders	**18 (3.8)/ [4.1]**	**7 (2.5)/ [2.7]**	**46 (3.8)/ [2.0]**	**3 (4.7)/ [5.5]**	**56 (3.6)/ [2.2]**
Insomnia	5 (1.1)/ [1.1]	1 (0.4)/ [0.4]	16 (1.3)/ [0.7]	1 (1.6)/ [1.8]	18 (1.2)/ [0.7]
Reproductive system and breast disorders	**59 (12.4)/ [13.3]**	**42 (14.9)/ [16.0]**	**215 (18.0)/ [9.5]**	**12 (18.8)/ [21.9]**	**269 (17.4)/ [10.4]**
Cervical dysplasia	6 (1.3)/ [1.4]	8 (2.8)/ [3.1]	40 (3.3)/ [1.8]	0	48 (3.1)/ [1.9]
Hot flush	13 (2.7)/ [2.9]	7 (2.5)/ [2.7]	36 (3.0)/ [1.6]	5 (7.8)/ [9.1]	48 (3.1)/ [1.9]
Vaginal discharge	6 (1.3)/ [1.4]	9 (3.2)/ [3.4]	27 (2.3)/ [1.2]	2 (3.1)/ [3.6]	38 (2.5)/ [1.5]
Vaginal haemorrhage	6 (1.3)/ [1.4]	4 (1.4)/ [1.5]	19 (1.6)/ [0.8]	0	23 (1.5)/ [0.9]
Vulvovaginal burning sensation	8 (1.7)/ [1.8]	1 (0.4)/ [0.4]	16 (1.3)/ [0.7]	4 (6.3)/ [7.3]	21 (1.4)/ [0.8]
Vulvovaginal pruritus	8 (1.7)/ [1.8]	6 (2.1)/ [2.3]	18 (1.5)/ [0.8]	5 (7.8)/ [9.1]	29 (1.9)/ [1.1]
Respiratory, thoracic and mediastinal disorders	**14 (3.0)/ [3.2]**	**9 (3.2)/ [3.4]**	**44 (3.7)/ [1.9]**	**8 (12.5)/ [14.6]**	**61 (4.0)/ [2.4]**
Cough	2 (0.4)/ [0.5]	3 (1.1)/ [1.1]	17 (1.4)/ [0.8]	1 (1.6)/ [1.8]	21 (1.4)/ [0.8]
Vascular disorders	**4 (0.8)/ [0.9]**	**1 (0.4)/ [0.4]**	**22 (1.8)/ [1.0]**	**0**	**23 (1.5)/ [0.9]**
Hypertension	4 (0.8)/ [0.9]	0	17 (1.4)/ [0.8]	0	17 (1.1)/ [0.7]

1: Subjects were counted only once within each preferred term. 2: Including data of 0.25%, 0.50% and 1.0% DHEA doses from studies ERC-210, ERC-213, ERC-230 (up to Week 52), ERC-231, ERC-234 and ERC-238. Data from 10

subjects treated for 1 week with 1.8% DHEA in ERC-213 are not included. 3: TEAE (treatment-emergent adverse event): Any event that starts or worsens after the start of study treatment through 30 days after the last dose of study treatment. (AEs coded with MedDRA version 16.1.) Note: Days at risk=cumulative number of days TEAEs could have been observed. Note: Incidence rate [IR] = 16 week incidence rate defined as the total number of events divided by the cumulative days at risk, multiplied by 114 days, multiplied by 100.

Treatment related adverse event (adverse drug reaction) overview

An overview of treatment related TEAEs is shown in Table 9.

Table 9: Overview of drug-related treatment-emergent adverse events by Primary System Organ Class and Preferred Term (safety population)

Primary System Organ Class Preferred term	Placebo N=474	0.25%DHEA (3.25 mg) N=282	0.50%DHEA (6.5 mg) N=1196	1.0%DHEA (13.0 mg) N=64	Overall[1] N=1542
Number (%) of subjects with at least one drug-related[2] TEAE[3]	18 (3.8)	12 (4.3)	110 (9.2)	0	122 (7.9)
Gastrointestinal disorders	**0**	**0**	**1 (0.1)**	**0**	**1 (0.1)**
Nausea	0	0	1 (0.1)	0	1 (0.1)
General disorders and administration site conditions	**16 (3.4)**	**11 (3.9)**	**99 (8.3)**	**0**	**110 (7.1)**
Application site discharge	16 (3.4)	11 (3.9)	98 (8.2)	0	109 (7.1)
Application site pain	0	0	2 (0.2)	0	2 (0.1)
Nervous system disorders	**0**	**0**	**2 (0.2)**	**0**	**2 (0.1)**
Headache	0	0	2 (0.2)	0	2 (0.1)
Psychiatric disorders	**1 (0.2)**	**0**	**1 (0.1)**	**0**	**1 (0.1)**
Aggression	1 (0.2)	0	0	0	0
Libido increased	0	0	1 (0.1)	0	1 (0.1)
Mood altered	1 (0.2)	0	0	0	0
Reproductive system and breast disorders	**2 (0.4)**	**1 (0.4)**	**10 (0.8)**	**0**	**11 (0.7)**
Hot flush	1 (0.2)	1 (0.4)	1 (0.1)	0	2 (0.1)
Vaginal discharge	0	0	1 (0.1)	0	1 (0.1)
Vaginal haemorrhage	0	0	1 (0.1)	0	1 (0.1)
Vaginal odour	0	0	1 (0.1)	0	1 (0.1)
Vulvovaginal burning sensation	0	0	4 (0.3)	0	4 (0.3)
Vulvovaginal discomfort	0	0	1 (0.1)	0	1 (0.1)
Vulvovaginal pruritus	1 (0.2)	0	1 (0.1)	0	1 (0.1)
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (0.1)**	**0**	**1 (0.1)**
Hypertrichosis	0	0	1 (0.1)	0	1 (0.1)

[1] Including data of 0.25%, 0.50% and 1.0% DHEA doses from studies ERC-210, ERC-213, ERC-230 (up to Week 16), ERC-231, ERC-234 and ERC-238. Data from 10 subjects treated for 1 week with 1.8% DHEA in ERC-213 are not included.

[2] Relationship based on the Investigator's judgement; it is the Sponsor's opinion that the only drug-related TEAE was application site discharge and increased libido.

[3] TEAE (treatment-emergent adverse event): Any event that starts or worsens after the start of study treatment through 30 days after the last dose of study treatment. (AEs coded with MedDRA version 16.1.)

Deaths

No deaths were recorded in the six clinical studies included in the analysis.

Serious adverse events

Serious adverse events (SAE) were reported for a comparable proportion of subjects in 0.50% DHEA group (1.3%) and placebo group (1.1%) up to Week 16.

Adverse events of special interest

Adverse events of interest in terms of oestrogenic and androgenic effects were evaluated.

Cervical dysplasia

Overall, there appeared to be 23 cases of interest (n = 11 detected by Pap smear and n = 12 by vaginal smear), for which 8 cases had colposcopic assessment. No further follow-up information was available for the remaining cases.

As cervical abnormalities were exclusion criteria in the studies, all subjects had normal Pap smear at screening, and the abnormalities occurred during treatment with prasterone, the overseas evaluator stated that 'the causal relationship is considered at least possible'. 'Abnormal pap smear (ASCUS)' was included as an Important identified risk in the risk management plan (RMP).

Endometrial safety

There were no clinically significant histologic findings. The sponsor stated the subject with disordered proliferative endometrium, and subject with functional polyp both had 'estrogen signature' typical of oestrogen use. Additional questions relating to transvaginal ultrasound results and missing data were considered resolved with responses during the overseas evaluation. Overall, there were no concerns regarding endometrial safety.

The results presented are in line with the TGA adopted EU guidelines for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women for endometrial safety which state for a new HRT a reasonable requirement is that the incidence of endometrial events should be statistically less than 2% after 1 year of treatment.

Breast safety

In Study ERC-230, of 434 subjects with an end-of-study mammogram, 431 (99%) had normal or no significant finding. There was one SAE of breast cancer (final histologic diagnosis of infiltrating carcinoma) considered possibly related to DHEA by the investigator, and one case of breast hyperplasia (final histologic diagnosis of atypical intraductal epithelial hyperplasia with micropapillary architecture) considered not related to study drug by the Investigator. However, taking into consideration pre-clinical data, and cases observed in clinical trials, the long-term use of prasterone in postmenopausal women with regard to breast safety was considered of concern. There was 1 case of ovarian cancer in the DHEA 0.50% group. The overseas evaluator stated no firm conclusion could be drawn given the limited number of cases of breast and ovarian cancer, however the role of prasterone in hormonal dependant cancers could not be excluded, stating further 'breast and ovarian cancers constitute a potential safety concern which warrants inclusion in the safety specification of the RMP as an important potential risk'.

Post-market

There were eight periodic safety update reports (PSUR) for reporting intervals from 16 November 2016 (IBD) to 21 November 2021, with corresponding Pharmacovigilance Risk Assessment Committee (PRAC) PSUR Assessment Reports and PRAC Recommendations provided in sponsor submitted dossier.

There were no new safety issues for Intrarosa identified, noting the assessments are based on the known safety concerns of Intrarosa (identified risks, potential risks and missing information) as outlined in the Risk management plan.

Risk management plan

The sponsor has submitted EU-RMP version 1.7 (date 3 December 2021; data lock point (DLP) 18 November 2021) and Australia specific annex (ASA) version 1.0 (date 22 June 2022) in support of this application.

In response to TGA's questions the sponsor provided an updated EU-RMP version 1.8 (date 29 March 2023; DLP 28 March 2023) and an ASA version 1.0 (9 February 2023).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 10. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 10: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Abnormal Pap smear (ASCUS)	✓	–	✓	–
Important potential risks	Oestrogen-dependent cancers such as ovarian or breast cancer	✓	–	✓	–
Missing information	Long-term use (after 12 months)	✓	–	✓	–
	Use in women with active or past oestrogen-dependent malignant tumours (breast and endometrial cancer)	✓	–	✓	–
	Use in women with gynaecological findings (including uterine fibroids, abnormal Pap smear (ASCUS), untreated endometrial hyperplasia or undiagnosed genital bleeding)	✓	–	✓	–
	Use in women with cardiovascular disease or uncontrolled hypertension (blood pressure above 140/90 mmHg)	✓	–	✓	–
	Use in women with current or previous thromboembolic disease (either arterial or venous)	✓	–	✓	–
	Women with a current hormonal treatment: hormone replacement therapy (e.g. oestrogen alone or combined with progestogens or androgen treatment)	✓	–	✓	–

ASCUS - Atypical Squamous Cells of Undetermined Significance

The summary of safety concerns is acceptable from an RMP perspective. This summary of safety concerns is the same as the summary approved by the EMA.

Only routine pharmacovigilance has been proposed for Australia. The pharmacovigilance plan is acceptable from an RMP perspective.

Only routine risk minimisation activities have been proposed for Australia. This is in line with the approached carried out in the EU. Risk minimisation plan is acceptable.

Recommended condition/s of registration

The suggested wording is:

> 'The Intrarosa EU-RMP (version 1.8, date 29 March 2023; DLP 28 March 2023), with ASA (version 1.0, dated 9 February 2023), included with submission PM-2022-02509-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.'

The following wording is recommended for the PSUR requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.'

The following wording is recommended for the Black Triangle Scheme condition of registration:

> 'Intrarosa (prasterone) is to be included in the Black Triangle Scheme. The PI and CMI for Intrarosa must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.'

Risk-benefit analysis

Delegate's considerations

Efficacy

Following treatment with intravaginal DHEA 0.50% (6.5 mg prasterone; Intrarosa) for 12 weeks, statistically significant differences for DHEA 0.50% versus placebo were demonstrated for the four co-primary endpoints in both pivotal studies. The pivotal studies included subjects with moderate to severe symptoms. There are no data for women with mild symptoms.

The studies were placebo controlled in line with United States Food and Drug Administration guidance. The efficacy of prasterone compared to standard of care (intravaginal oestrogens) has not been demonstrated.

The treatment effect on the clinical co-primary endpoint dyspareunia was modest. There was a placebo effect for this endpoint demonstrated in both studies, potentially related to lubricant-like effect of the excipient.

Safety

1196 postmenopausal women were treated with prasterone 6.5 mg (Intrarosa) during the clinical trial program, including 435 receiving treatment for 52 weeks.

Treatment-emergent adverse events assessed as drug related by the investigator up to Week 16 were reported for a higher proportion of subjects in 0.5% DHEA group than placebo group; 9.2% versus 3.8%. Application site discharge was the most frequent treatment-related AE (8.2% vs. 3.4%), with all other PTs reported for ≤ 0.3% subjects. The overseas evaluator considered frequent local adverse events (AE) not related or possibly related to prasterone seemed likely related to prasterone pharmaceutical form, and other TEAEs assessed as non-related or possibly related by the investigator could be related to prasterone based on oestrogenic effects (cervical dysplasia, hormonal tumour development [breast, ovarian], uterine/cervical polyps, weight fluctuations, breast mass, breast tenderness) and androgenic effects (hypertension).

Systemic exposure

Pharmacokinetics data demonstrated systemic exposure to DHEA and metabolites with intravaginal prasterone treatment, with concentrations within the expected range for postmenopausal women.

Long-term safety

There is a lack of safety data beyond 12 months of use. Further, given the exclusion criteria of the clinical trials, there were limited long-term safety data in the intended patient population. It is not unreasonable to expect excluded co-morbidities such as coronary artery disease, hypertension, gynaecological abnormalities or history of cancer may be present in postmenopausal women.

The TGA evaluator considers the Summary of Safety Concerns in the EU-RMP and Summary of Product Characteristic sufficiently characterise the risks with prasterone identified during the COR evaluation procedure. The uncertainties regarding long-term safety were mitigated with modifications to labelling and Safety Concerns in the RMP.

Additional issues not part of the original application

It appears that the sponsor intended to register a 28-pessary starter pack (Therapeutic Goods Order No. 91 terminology for sample pack) additional to the 28-pessary trade pack during the application. However, the starter pack was not part of the original application within PM-2022-02509-1-5. The proposal to register said starter pack was only introduced in a later sequence, but a corresponding application form had not been received.

Therapeutic Goods Order No. 91 limits the starter pack size to be not exceeding one third the size of the trade pack. Such a smaller pack may have been considered within this application, but a 28-pessary starter pack could not be considered within this application.

Proposed action

The benefit-risk balance is not favourable for the indication initially proposed by the sponsor:

Intrarosa is indicated for the treatment of postmenopausal vulvovaginal atrophy.

This indication is not aligned with the COR indication. Subsets of the COR indications, or a difference in wording of the COR indication that retains the same meaning can be accommodated within a COR-B pathway, but not an indication broader than the COR indication.

Consequently, the sponsor was advised to change the indication to the following:

Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

For this revised indication, the benefit-risk balance is favourable. This has been reflected in an updated PI document.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Intrarosa (prasterone) 6.5 mg, pessary, blister pack, indicated for:

Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

Specific conditions of registration applying to these goods

- Intrarosa (prasterone) is to be included in the Black Triangle Scheme. The PI and CMI for Intrarosa must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Intrarosa EU-RMP (version 1.8, date 29 March 2023; DLP 28 March 2023), with ASA (version 1.0, dated 9 February 2023), included with submission PM-2022-02509-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Intrarosa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #