

From: s 22
To: [Signal Investigation Coordinator](#)
Cc: [AEReporting.AUS](#); s 22 (Pfizer); s 22
Subject: RE: [EXTERNAL] Medicine safety notification: Pfizer Australia Pty Ltd : Off-label use of Nafarelin for puberty suppression in children and young people under 18 years of age for gender incongruence
Date: Friday, 20 June 2025 3:29:54 PM
Attachments: [image001.png](#)
[25-0232_NAFARELIN_WORD-TRX-SMT-10489.pdf](#)

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Dear TGA,

Please find attached Pfizer's signal assessment.

Should you have any questions or require further information relating to this matter, please do not hesitate to contact me.

Kind regards,

s 22

[Redacted signature block]



I acknowledge and respect the Traditional Lands of all Aboriginal People. I acknowledge that Aboriginal People are the first people of this country. I pay my respects to all Elders past, present and future. I ask all those that walk, work and live on traditional Aboriginal Lands to be respectful of culture and traditions.

LEGAL NOTICE Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this e-mail by anyone else is unauthorised. If you are not an addressee, any disclosure or copying of the contents of this e-mail or any action taken (or not taken) in reliance on it is unauthorised and may be unlawful. If you are not an addressee, please inform the sender immediately. Pfizer Australia has its registered office at Level 17, 151 Clarence Street, Sydney, NSW, 2000

From: Therapeutic Goods Administration (TGA) **On Behalf Of** si.coordinator@health.gov.au

Sent: Friday, 20 June 2025 3:25 PM

To: s 22

Cc: AEReporting,AUS

Subject: [EXTERNAL] Medicine safety notification: Pfizer Australia Pty Ltd : Off-label use of Nafarelin for puberty suppression in children and young people under 18 years of age for gender incongruence

Submitted on Fri, 2025-06-20 15:21

Submitted by: Anonymous

Remember, please reply to this email and attach relevant supporting documents if required.

Submitted values are:

Reporter details

Reporting sponsor

Pfizer Australia Pty Ltd

Reporters name

s 22

Contact email address

s 22

Secondary contact email address

AUS.AEReporting@pfizer.com

Issue details

Safety issue

Off-label use of Nafarelin for puberty suppression in children and young people under 18 years of age for gender incongruence

Type of safety issue

OSI - Other safety issue

Date of local awareness by the sponsor (Day 0)

2025-05-28

Type of notification

Initial

Product details

Is your company the product innovator?

Yes

Product details

- **Product name:** SYNAREL NASAL SPRAY nafarelin 2mg/mL (as acetate) spray solution aerosol pump actuated metered dose
ARTG no.: 48127
Active ingredient(s): Nafarelin
Australian sponsor: Pfizer Australia Pty Ltd
Marketed in Australia: Yes

Issue source

Safety issue source

Comparable overseas regulator

Safety issue summary

On 13-May-2025, Pfizer received a notification from MHRA for signal of Off-label use of Nafarelin for puberty suppression in children and young people under 18 years of age for gender incongruence. A signal evaluation was opened by above country Pfizer colleagues and the signal was validated on 13-May-2025. Review of the signal concluded on 26-May-2025 and was considered refuted. Notification of the outcome of the signal assessment from above country colleagues was received 28-May-2025.

Medical Literature

Search Methodology

A cumulative literature search was performed till 14 May 2025 to identify publications involving puberty suppression and gender dysphoria with nafarelin in children and young people under 18 years of age using the following databases: Databases included: Embase and Ovid Medline

Pfizer Post-Marketing Safety Data

Search Methodology

The Pfizer global safety database was searched cumulatively through 12 May 2025 to identify cases reporting the suspect drug Nafarelin and Medical Dictionary for Regulatory Activities (MedDRA) (Version. 28) high level term (HLT) "Off label use", co-reporting the adverse event Preferred term (PT) "gender dysphoria" or co-reporting the indication PT "gender dysphoria".

Conclusion (Description of Risk, Summary of Actions)

Based on the available data from the literature and the safety database, nafarelin, has rarely been used for gender dysphoria/gender incongruence. There are no consistent findings regarding the effect of nafarelin across the articles. There is still a lack of robust evidence to determine the impact of nafarelin for gender dysphoria/gender incongruence. In conclusion, no new safety information was identified from the review of medical literature. Following a comprehensive review of the nafarelin cases, no new safety information has been identified regarding the nafarelin cases of off-label use for gender dysphoria and gender incongruence retrieved from the safety database. This assessment is based on the evaluation of the nafarelin target population cases versus the retrieved nafarelin off-label population cases.

No new safety findings were identified for nafarelin that would warrant updating the RSI

(reference safety information).

MAH will continue monitoring the off-label uses of nafarelin through routine pharmacovigilance.

Other actions

Do you intend to update your Australian Product Information document?

No

Are you considering any other actions?

No

Supporting documents

Attachments

You will receive a copy of your submission to the contact email address provided.

When you receive this email, **please reply and attach any relevant supporting documents**, for example:

- sponsor assessment
- comparable overseas regulator assessment report
- any other relevant assessments

Product Name

NAFARELIN

Signal Description

Off-label use of Nafarelin for puberty suppression in children and young people under 18 years of age for gender incongruence.

Primary Source

Enquiry from a Regulatory Authority
Board Of Health (BoH): MHRA

Date Signal Validated

13-May-2025

Date Completed

26-May-2025

Safety Signal Analysis

Medical Literature

Search Methodology

A cumulative literature search was performed till 14 May 2025 to identify publications involving puberty suppression and gender dysphoria with nafarelin in children and young people under 18 years of age using the following databases: Databases included: Embase and Ovid Medline

Analysis

A cumulative search was performed till 14 May 2025 to identify publications involving puberty suppression and gender dysphoria with nafarelin in children and adolescents under 18 years of age using Embase and Ovid Medline (R) Databases which yield 6 publications out of those 1 was considered not relevant since there was no information available on off-label uses of nafarelin for puberty suppression. The SRL (safety risk lead) presented the remaining 5 relevant articles. All articles provided limited information.

1. Krebs et al presented a review of existing literature on gender-affirming care for transgender and gender-diverse (TGD) young people (children, adolescents and young adults) including both medical and non-medical interventions. The medical interventions include gonadotropin releasing hormone analogs (GnRHa) also known as puberty blockers, gender-affirming hormones (GAH), anti-androgen therapies and menstrual suppression. The GnRHa can be used to prevent the progression of secondary sex characteristics and are also associated with reduced breast development in transmasculine individuals and reduced penile size in transfeminine individuals. GnRHa therapy is also useful in decreasing the behavioral, emotional symptoms and depressive symptoms, and increase in global psychological functioning, though it has not been associated with reductions in gender dysphoria. In the article, it is reported that nafarelin is available as a GnRHa that can be administered as a nasal spray (4 times a day) at a dose of 1600 to 1800 µg/day.

MAH comment: The review relies on existing studies, many of which are based on treatments for transgender adults or other groups (e.g., pubertal suppression in children with precocious puberty). The review acknowledges that the long-term effects of puberty blockers and gender-affirming hormones on growth, bone health, cardiovascular health, and fertility are not yet fully understood.

2. Grimstad et al presented a retrospective cohort study for breakthrough bleeding in transgender and gender diverse adolescents and young adults (TGD AYA) who were on long-term (more than 1 year) testosterone gender-affirming hormone therapy (T-GAHT). Of the 367 TGD patients seen for T-GAHT in the study period, 232 patients met the final inclusion criteria for whom the age range for T-GAHT initiation was 13-28 years. Breakthrough bleeding started at mean of 24.3 ± 17.2 months after initiation of testosterone, of which, 79.3% (n=46) had no known cause, 17.2% (n=10) bled only with missed T-GAHT doses, and 3.4% (n=2) bled only when withdrawing from concomitant menstrual suppression. There were no significant differences between patients with and without breakthrough bleeding in terms of age of T-GAHT initiation, body mass index, race/ethnicity, testosterone type used, use of additional menstrual suppression, or serum testosterone or estradiol levels. Endometriosis was nearly 10 times more common in the patients who had breakthrough bleeding. Also, no single method of managing breakthrough bleeding was found to be superior to others. All 8 patients who continued GnRHa maintained amenorrhea. The results of the study suggest that breakthrough bleeding is relatively common in transgender and gender diverse adolescents and young adults on long-term T-GAHT, even after initial amenorrhea, and that most cases do not have an identifiable cause. There was limited information available regarding nafarelin whether it was given to the subjects included in the study. It was only reported that nafarelin as a GnRHa can be used as a nasal spray (1-2 sprays twice a day). The publication also states that nafarelin achieves 90% amenorrhea at 3 months of use.

MAH comment: The study focuses on patients from a single tertiary-care children's hospital (Boston, Massachusetts, Department of Obstetrics, Gynecology, and

Reproductive Biology, Pediatrics, Harvard Medical School) , which may not represent the broader transgender and gender-diverse population.

3. Schmidt et al provided a comprehensive overview of psychological outcomes and reproductive issues for cases with gender dysphoria, particularly focusing on transgender youth and adolescents. The onset of worsening gender dysphoria during puberty significantly predicts the persistence of transgenderism throughout adulthood. As per the World Professional Association for Transgender Health (WPATH) and the Endocrine Society, pubertal suppression therapy is recommended to be initiated at Tanner Stage 2 for adolescents with gender dysphoria. If there is prevention of the development of secondary sexual characteristics that are not consistent with a person's preferred gender, they can lead to decreased body dysphoria and lessen the need for future surgical reconstruction. Pubertal suppression is typically achieved using GnRH analogues. However, there are concerns about potential detrimental effects of GnRH analogues on bone mineralization and height. Overall, treatment options for dysphoria may include puberty suppression, cross-sex hormones, and gender reassignment surgery, which aim to align physical characteristics with gender identity. The article mentioned nafarelin intranasal spray in multiple daily doses as one of the interventions available for pubertal suppression in transgender adolescents. However, it has not yet been used for gender dysphoria.

MAH comment: Although this longitudinal study is applicable to gender nonconforming adolescents globally, limited research has been conducted in regard to psychological functioning among young transgender individuals.

4. Rosenthal et al reviewed key aspects on the biological underpinnings of gender identity, the epidemiology and natural history of transgenderism, current clinical practice guidelines for transgender youth, and limitations and challenges to optimal care. There were 2 case reports in the article. The case 1 reported a 13-year-old phenotypic male who identified as female from a very young age. The patient experienced anxiety and depression, which worsened with onset of puberty. After mental health evaluations, the patient was prescribed GnRH agonist treatment to suppress puberty, but this was denied by insurance. Case 2 reported a 16-year-old phenotypic female who identified as male. The patient experienced significant anxiety, depression and suicidal ideation, especially after puberty onset. After evaluation, the patient was treated with GnRH agonists to suppress the menstrual cycle, followed by testosterone therapy. This led to resolution of gender dysphoria and suicidal ideation, and reduced depression.

Results of these studies depict the concept that gender identity is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors. The transgender youth are seeking medical services to enable development of physical characteristics consistent with their gender using puberty blockers such as GnRH agonists at Tanner stage 2/3 for youth with persistent gender dysphoria, cross-sex hormones around the age of 16 years, surgical procedures until age 18. It was reported that nafarelin can be used intranasally in multiple daily doses for inhibiting gonadal sex steroid secretion in transgender youth.

MAH comment: Limited safety and efficacy data currently exist, with virtually no published data on the use of pubertal blockers in gender-dysphoric individuals less than 12 years of age or cross-sex hormones in transgender youth less than 16 years of age.

5. Nakatsuka et al presented an overview of endocrine treatment for transgender individuals and discuss the assessment of cardiovascular risk factors associated with such treatment. This provides a brief overview of hormone regimens for both male-to-female (MTF) and female-to-male (FTM) transgender individuals, including types of hormones used, dosages, and administration routes which includes estrogen, antiandrogens and GnRH agonists. Transsexual adolescents (Tanner stage 2, age 11 years [9–13 years]) are treated by endocrinologists to suppress puberty with gonadotropin-releasing hormone (GnRH) agonists until 16 years of age, after which cross-sex hormones may be given. There was limited information available regarding nafarelin which stated that nafarelin can be used as one of the GnRH agonist in MTF transsexual hormone therapy as a nasal spray at a dose of 400 µg/day.

MAH comment: Limited long-term data on long-term effects of hormone therapy on heart health exist.

REFERENCES

1. Krebs D, Harris RM, Steinbaum A, Pilcher S, Guss C, Kremen J, Roberts SA, Baskaran C, Carswell J, Millington K. Care for Transgender Young People. *Horm Res Paediatr.* 2022;95(5):405-414.
2. Grimstad F, Kremen J, Shim J, Charlton BM, Boskey ER. Breakthrough Bleeding in Transgender and Gender Diverse Adolescents and Young Adults on Long-Term Testosterone. *J Pediatr Adolesc Gynecol.* 2021 Oct;34(5):706-716.
3. Schmidt L, Levine R. Psychological Outcomes and Reproductive Issues Among Gender Dysphoric Individuals. *Endocrinol Metab Clin North Am.* 2015 Dec;44(4):773-85.
4. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metab.* 2014 Dec;99(12):4379-89
5. Nakatsuka M. Endocrine treatment of transsexuals: assessment of cardiovascular risk factors. *Expert Review of Endocrinology & Metabolism.* 2010;5(3):319–322.

Pfizer Post-Marketing Safety Data

Search Methodology

The Pfizer global safety database was searched cumulatively through 12 May 2025 to identify cases reporting the suspect drug Nafarelin and Medical Dictionary for Regulatory Activities (MedDRA) (Version. 28) high level term (HLT) “Off label use”, co-reporting the adverse event Preferred term (PT) “gender dysphoria” or co-reporting the indication PT “gender dysphoria”.

Analysis

A total of 8 cases were retrieved using the above strategy. All were from spontaneous sources and non-serious. Cases were reported from United Kingdom (6) and Japan and US (1 each).

Minimum age was reported at 12 years old and maximum age was reported at 45 years old (Mean age=28.5-year, Standard Deviation=23.3 , n=2). (The case from Japan, AER: 2015471982, was in her 50s (reported as “5-decade-old female patient”), so it is not relevant to the topic for children and young people under 18 years of age and will not be evaluated. Concomitant products/co-suspect medication information was unknown in all cases. Medical history was unknown in all cases. Case outcome was unknown (8).

AER number/ Age/ Gender/ Country/ Source	Medical history	Co-suspect/ Concomitant medications	Preferred term/ indication	Summary and MAH Comment:
2019509118/ 12/ female/ US/ spontaneous	not reported	not reported not reported	Off label use Gender dysphoria	<p>This is a spontaneous report of a 12-year-old female patient who started to receive nafarelin acetate for gender dysphoria at a dose 2 sprays (400 mcg), into each nostril, twice per day. Medical history and concomitant medications were not reported. The outcome of the event of “off label use” was unknown. The action taken was not applicable.</p> <p>MAH Comment: This case report revealed the use of Nafarelin for gender dysphoria which is off label use of medication since it is not present in the Pfizer’s label. Case does not provide sufficient information.</p>

<p>2021038735/ No data/ No data/ United Kingdom/ spontaneous</p>	<p>not reported</p>	<p>not reported not reported</p>	<p>Off label use Gender dysphoria</p>	<p>This is a spontaneous report received from a contactable consumer. This consumer reported similar events for 6 patients. This is the first of six reports.</p> <p>Medical history and concomitant medications were not reported. The outcome of the event of “off label use” was unknown. The action taken was not applicable.</p> <p>MAH Comment: This case report revealed the use of Nafarelin for gender dysphoria which is off label use of medication since it is not present in the Pfizer’s label. Case does not provide sufficient information.</p>
<p>2021142415/ No data/ No data/ United Kingdom/ spontaneous</p>	<p>not reported</p>	<p>not reported not reported</p>	<p>Off label use Gender dysphoria</p>	<p>This is a spontaneous report received from a contactable consumer. This consumer reported similar events for 6 patients (this is case 2 of 6). Medical history and concomitant medications were not reported. The outcome of the event of “off label use” was unknown. The action taken was not applicable.</p> <p>MAH Comment: This case report revealed the use of Nafarelin for gender dysphoria which is off label use of medication since it is not present in the Pfizer’s label.</p>

				Case does not provide sufficient information.
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AER number/ Age/ Gender/ Country/ Source	Medical history	Co-suspect/ Concomitant medications	Preferred term/ indication	Summary and MAH Comment:
2021142413/ No data/ No data/ United Kingdom/ spontaneous	not reported	not reported not reported	Off label use Gender dysphoria	<p>This is a spontaneous report received from a contactable consumer who reported similar events for 6 patients (this is case 3 of 6). Medical history and concomitant medications were not reported. The outcome of the event of “off label use” was unknown. The action taken was not applicable.</p> <p>MAH Comment: This case report revealed the use of Nafarelin for gender dysphoria which is off label use of medication since it is not present in the Pfizer’s label. Case does not provide sufficient information.</p>
2021142414/ No data/ No data/ United Kingdom/ spontaneous	not reported	not reported not reported	Off label use Gender dysphoria	<p>This is a spontaneous report received from a contactable consumer, who reported similar events for 6 patients (this is case 4 of 6). Medical history and concomitant medications were not reported. The outcome of the event of “off label use” was unknown. The action taken was not applicable.</p>

				<p>MAH Comment: This case report revealed the use of Nafarelin for gender dysphoria which is off label use of medication since it is not present in the Pfizer's label. Case does not provide sufficient information.</p>
<p>2021142411/ No data/ No data/ United Kingdom/ spontaneous</p>	<p>not reported</p>	<p>not reported not reported</p>	<p>Off label use Gender dysphoria</p>	<p>This is a spontaneous report received from a contactable consumer, who reported similar events for 6 patients (this is case 5 of 6). Medical history and concomitant medications were not reported. The outcome of the event of "off label use" was unknown. The action taken was not applicable.</p> <p>MAH Comment: This case report revealed the use of Nafarelin for gender dysphoria which is off label use of medication since it is not present in the Pfizer's label. Case does not provide sufficient information.</p>
<p>2021142412/ No data/ No data/ United Kingdom/ spontaneous</p>	<p>not reported</p>	<p>not reported not reported</p>	<p>Off label use Gender dysphoria</p>	<p>This is a spontaneous report received from a contactable consumer, who reported similar events for 6 patients (this is case 6 of 6). Medical history and concomitant medications were not reported. The outcome of the event of "off label use" was unknown. The action taken was not applicable.</p>

				<p>MAH Comment: This case report revealed the use of Nafarelin for gender dysphoria which is off label use of medication since it is not present in the Pfizer’s label. Case does not provide sufficient information.</p>
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Analysis and Data Assessment

Background: In May 2025, MHRA and the Department of Health and Social Care (DHSC) continued a [targeted consultation](#) on proposed changes to the availability of gonadotropin-releasing hormone (GnRH) analogues, also known as “puberty blockers”. As part of this consultation, the Secretary of State for Health and Social Care and the Minister of Health for Northern Ireland jointly [consulted the Commission on Human Medicines \(CHM\)](#) on these proposals and contacted Pfizer for the GnRH analogue nafarelin to present any relevant information in relation to the off-label use of these medicines for puberty suppression in children and young people under 18 years of age for gender incongruence.

According to Pfizer’s label, the use of nafarelin for gender dysphoria/gender incongruence is considered off-label, as this indication has not been evaluated in clinical trials, and there is insufficient evidence to confirm its efficacy and safety in this context.

Literature review: A cumulative search was performed till 14 May 2025 to identify publications involving puberty suppression and gender dysphoria with nafarelin in children and adolescents under 18 years of age using Embase and Ovid Medline (R) Databases which yield 6 publications out of those 1 was considered not relevant since there was no information available on off-label uses of nafarelin for puberty suppression. The SRL presented the remaining 5 relevant articles. All articles provided limited information.

Pfizer safety database review: The Pfizer global safety database was searched cumulatively through 12 May 2025 using Medical Dictionary for Regulatory Activities (MedDRA) (Version. 28) to retrieve cases of suspect drug nafarelin with high level term (HLT) “Off label use”, co-reporting the adverse event Preferred term (PT) “gender dysphoria) or co-reporting the indication PT “gender dysphoria”. The search retrieved a total of 8 cases, among them, 1 from Japan was found not relevant due to the age of 45 years of patient. All were spontaneous non-serious cases reported from United Kingdom (6) and the US (1 each). No information was provided on concomitant medication, concurrent condition, medical history, and none of them was found to be associated with any potential adverse event.

Conclusion: Based on the available data from the literature and the safety database, nafarelin, has rarely been used for gender dysphoria/gender incongruence. There are no consistent findings regarding the effect of nafarelin across the articles. There is still a lack of robust evidence to determine the impact of nafarelin for gender dysphoria/gender incongruence. In conclusion, no new safety information was identified from the review of medical literature. Following a comprehensive review of the nafarelin cases, no new safety information has been identified regarding the nafarelin cases of off-label use for gender dysphoria and gender incongruence retrieved from the safety database. This assessment is based on the evaluation of the nafarelin target population cases versus the retrieved nafarelin off-label population cases.

No new safety findings were identified for nafarelin that would warrant updating the RSI. The signal will be refuted.

Based on the totality of the reviewed data, the MAH is going to continue monitoring the off-label uses of nafarelin through routine pharmacovigilance.

Conclusion (Description of Risk, Summary of Actions)

Based on the available data from the literature and the safety database, nafarelin, has rarely been used for gender dysphoria/gender incongruence. There are no consistent findings regarding the effect of nafarelin across the articles. There is still a lack of robust evidence to determine the impact of nafarelin for gender dysphoria/gender incongruence. In conclusion, no new safety information was identified from the review of medical literature. Following a comprehensive review of the nafarelin cases, no new safety information has been identified regarding the nafarelin cases of off-label use for gender dysphoria and gender incongruence retrieved from the safety database. This assessment is based on the evaluation of the nafarelin target population cases versus the retrieved nafarelin off-label population cases.

No new safety findings were identified for nafarelin that would warrant updating the RSI (reference safety information).

MAH will continue monitoring the off-label uses of nafarelin through routine pharmacovigilance.

Category of Risk

Signal Refuted
Important: NA

Safety Assessment for Medicines

Medicines Surveillance and Signal Investigation Section (MSSIS)



Australian Government

Department of Health,
Disability and Ageing

Date completed by Evaluator

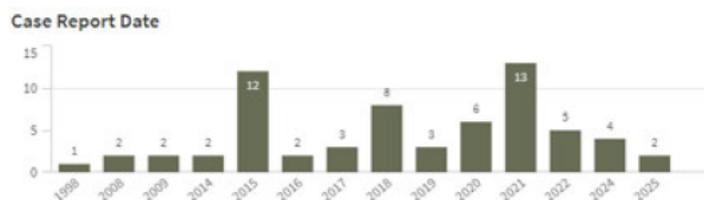
22 April 2025

Safety of 'Puberty Blockers' (gonadotrophin-releasing hormone analogues/GnRH agonists)

Issue for Assessment	<p><u>Issue description</u></p> <p>On 11 December 2024, the United Kingdom (UK) government published an article on the indefinite ban of puberty-suppressing hormones (gonadotrophin-releasing hormone [GnRH] analogues, also known as GnRH agonists) for the treatment of gender incongruence and/or gender dysphoria in children¹.</p> <p>This was based on independent expert advice from the UK's Commission on Human Medicines (CHM) that there is currently an unacceptable safety risk in the continued prescription of puberty blockers to children.</p> <p><u>Issue history</u></p> <p>This issue has not been previously investigated. A related signal was identified in Content Manager: 'Safety of leuprorelin acetate (Lucrin/Eligard) for the treatment of central precocious puberty in children and bone mineral density loss' (Content Manager: E19-543238).</p> <ul style="list-style-type: none"> The product information (PI) document for LUCRIN DEPOT contains information about the risk of bone mineral density loss in children. The PI for ELIGARD contains general information about the risk of bone mineral density loss, but this is not specific to children. 												
Product details incl. indications and mechanism of action	<p><u>Indications for use in children:</u></p> <p>Central precocious puberty (CPP) is a registered indication for the following GnRH agonist-containing products:</p> <ul style="list-style-type: none"> ELIGARD (leuprorelin acetate) 45 mg 6 month - children aged 2 years and older. LUCRIN (leuprorelin acetate) Depot Paediatric 3-month 30 mg PDS injection. DIPHERELINE (triptorelin embonate) 22.5 mg 6-month formulation - children aged 2 years and older. <p>The use of GnRH agonists for the treatment of gender incongruence and/or gender dysphoria is considered off-label use in Australia.</p> <p>Other GnRH agonist-containing products registered in the Australian Register of Therapeutic Goods (ARTG) do not have approved indications in children, i.e. paediatric population less than 18 years of age. These products contain the active ingredients goserelin (monotherapy or in combination with bicalutamide), triptorelin acetate, leuprorelin in combination with bicalutamide, and nafarelin. Non-paediatric indications include the treatment of prostate cancer, endometriosis and in assisted reproduction.</p> <p><u>Mechanism of action:</u> GnRH agonists are luteinising hormone-releasing hormone (LH-RH) agonists that act as a potent inhibitor of gonadotrophin secretion when given continuously in therapeutic doses. After initial stimulation, chronic administration leads to suppression of ovarian and testicular steroidogenesis. The effects are generally reversible upon discontinuation.</p> <table border="1" data-bbox="347 1794 1522 2049"> <thead> <tr> <th>PRODUCT NAME</th> <th>Active ingredient</th> <th>ARTG Number</th> <th>Date of registration</th> <th>Sponsor</th> <th>Notes</th> </tr> </thead> <tbody> <tr> <td>ELIGARD 45 mg 6 month</td> <td>Leuprorelin acetate</td> <td>101581</td> <td>16/09/2005</td> <td>Mundipharma</td> <td>Restricted Pharmaceutical Benefit Scheme (PBS) benefit for the treatment of CPP</td> </tr> </tbody> </table>	PRODUCT NAME	Active ingredient	ARTG Number	Date of registration	Sponsor	Notes	ELIGARD 45 mg 6 month	Leuprorelin acetate	101581	16/09/2005	Mundipharma	Restricted Pharmaceutical Benefit Scheme (PBS) benefit for the treatment of CPP
PRODUCT NAME	Active ingredient	ARTG Number	Date of registration	Sponsor	Notes								
ELIGARD 45 mg 6 month	Leuprorelin acetate	101581	16/09/2005	Mundipharma	Restricted Pharmaceutical Benefit Scheme (PBS) benefit for the treatment of CPP								

	LUCRIN DEPOT Paediatric 3- month 30 mg PDS injection	Leuprorelin acetate	218936	13/10/2014	Abbvie	Restricted benefit (PBS) for the treatment of CPP
	DIPHERELINE 22.5 mg 6- month formulation	triptorelin embonate	159173	27/07/2010	Ipsen	Restricted benefit (PBS) for the treatment of CPP
Australian PI	<p><u>Usage:</u></p> <p>Usage data for off-label use of GnRH agonists for the treatment of gender-affirming care and/or gender dysphoria in Australia is not available.</p> <p>Safety information regarding the treatment of CPP in children including reported adverse events (AEs) are similar across the 3 products currently indicated for use in children (ELIGARD, LUCRIN DEPOT and DIPHERELINE). All PIs include advice that treatment of children for CPP should be under the supervision of a paediatric endocrinologist or paediatrician/endocrinologist with expertise in the treatment of CPP.</p> <p>Similar warnings across PIs (ELIGARD, LUCRIN DEPOT and DIPHERELINE):</p> <p><u>4.4 Special warnings and precautions for use</u></p> <ul style="list-style-type: none"> - Convulsions (post-marketing reports in paediatric patients) - Psychiatric events (emotional lability including irritability, anger, aggression, and depression) - Initial rise of gonadotropins and sex steroid levels (increase in clinical signs and symptoms of puberty including vaginal bleeding) - Pseudotumor cerebri/idiopathic intracranial hypertension (reported in paediatric patients) <p>Specific warnings in certain PIs:</p> <p><u>4.4 Special warnings and precautions for use</u></p> <ul style="list-style-type: none"> - Bone mineral density (may decrease during GnRH therapy in children with CPP) (LUCRIN) - Pituitary apoplexy, a clinical syndrome secondary to infarction of the pituitary gland (post-marketing reports) (LUCRIN DEPOT) - Future fertility (limited information) (DIPHERELINE) - Slipped capital femoral epiphysis after withdrawal of GnRH (DIPHERELINE) <p><u>Other listed AEs:</u></p> <p>In section <u>4.8 Adverse Effects</u>, several AEs are listed (across the 3 PIs) in relation to use in children/ CPP. The most common AEs listed include injection site reactions/pain, headache, abdominal pain, weight increased, vaginal bleeding, hypersensitivity, nasopharyngitis, pyrexia, cough, emotional lability, acne and hot flushes/sweating.</p> <p><u>Date of PIs:</u></p> <p>ELIGARD – 9 October 2024</p> <p>LUCRIN DEPOT – 21 February 2025</p> <p>DIPHERELINE – 11 December 2024</p>					
Overseas regulator labels	<p>Summary of Comparable Overseas Regulator (COR) labels: Safety information including advice/reported AEs (regarding use in children and treatment of CPP) is similar in COR labels when compared to Australian PIs (Aus PIs).</p>					

	COR	Review
	USPI FDA	<p>United States PIs are similar to AusPI.</p> <p>ELIGARD (leuprolide* acetate) 21/5/24 – not indicated for use in children (only for prostate cancer).</p> <p>LUPRON DEPOT (leuprolide* acetate) 21/3/24 - not indicated for use in children (only for prostate cancer).</p> <p>FENSOLVI (leuprolide* acetate) 17/10/24 – for CPP in children aged >2 years.</p> <p>Triptorelin embonate is not marketed in the US.</p> <p>TRIPTODUR (triptorelin pamoate) 12/7/22 – for CPP in children aged >2 years.</p> <p>*Note, in the US leuprorelin is termed leuprolide.</p>
	EU SmPC (Ireland)	<p>European Union SmPCs are similar to AusPIs.</p> <p>LUTRATE (leuprorelin acetate) August 2024.</p> <p>Triptorelin embonate not registered for use in children in the EU.</p> <p>DECAPEPTYL (triptorelin pamoate) November 2024.</p>
	Health Canada	<p>Canadian PMs are similar to AusPIs.</p> <p>ELIGARD (leuprolide* acetate) 26/1/24</p> <p>LUPRON DEPOT (leuprolide* acetate) 19/3/24</p> <p>Triptorelin embonate is not marketed in Canada. Triptorelin-containing products registered for use in children are not marketed in Canada.</p> <p>*Note, in Canada leuprorelin is termed leuprolide.</p>
	UK SmPC (MHRA)	<p>UK SmPCs are similar to AusPIs.</p> <p>LUTRATE (leuprorelin acetate) 17 July 2024.</p> <p>DECAPEPTYL (triptorelin pamoate) 7 November 2024.</p>
Australian adverse event reports (AEMS reports)	<p>Date: 22 April 2025 Default bookmark applied Generic name: leuprorelin, triptorelin, goserelin, nafarelin Reaction term: No filter applied Additional filters applied: Age less than 18 years Results: 65 reports</p> <p>Summary of Adverse Event Management System (AEMS) case review:</p> <p>Use/off-label use related to puberty suppression for gender-affirming care/dysphoria: Based on the information provided, no reports were identified for this use/within this context.</p> <p>Date range of reports in AEMS: 1998 to 2025</p> <p>Reports per year: apart from reporting spikes (see below), the range of reports received have been between 1 to 8 reports per year, with most years receiving between 2 to 5 reports.</p> <p>Spike in reports: 2015 (12 reports), 2021 (13 reports).</p>	

Figure 1. Total number of AEMS reports identified for GnRH agonists and age less than 18 years

During the 2 spikes in 2015 and 2021, it appears a number of reports were received by the same reporter for different patients. The majority of reports were for injection site reactions/pain at injection site (9 out of the 12 reports in 2015, 9 out of 13 reports in 2021). One duplicate report was identified in 2015, while 2 reports in 2021 were identified as being entered incorrectly for a paediatric patient when in fact the report refers to elderly male patients. The remaining reports were for gait disturbance after injection and anxiety.

Number of reports per active ingredient: leuprorelin (58), goserelin (4), triptorelin (2), nafarelin (1).

By age group: newborn (29 days of age and younger) (4), infant (>29 days and under 2 years) (1), child (2 to 11 years) (55), adolescent (12 to 17 years) (5).

The most commonly reported AEs were injection site reactions including pain, mass/swelling, infection and abscess (43).

No fatal outcomes were reported.

Literature Search

PubMed search

Date: 22 April 2025

Search terms: “puberty suppression gender safety”

Results: 29 articles were identified, of which **12 articles were relevant to this safety assessment (with one article in Japanese).**

The remaining articles were either not directly relevant to this safety assessment (related to the use of GnRH agonists for the treatment of CPP or other hormone-related conditions rather than use in gender-affirming care/gender dysphoria), or not relevant to this issue at all (2 articles, one on inhaled corticosteroid use and the other on pollutants in fish).

Summary of findings:

The 11 relevant articles (in English) that were identified consisted of:

- 5 reviews²⁻⁶ and 1 systematic review⁷ related to puberty suppression in children/adolescents in gender-affirming care/gender dysphoria
- 3 observational (retrospective) studies⁸⁻¹⁰ related to puberty suppression/GnRH agonist treatment in gender-affirming care/gender dysphoria
- 2 small cohort studies^{11, 12} looking at the efficacy and safety of puberty blockers/puberty induction in gender-affirming care/gender dysphoria.

Critical appraisal of these articles and a more detailed literature review may be considered if a specific drug-adverse event pair is identified for further investigation but is otherwise outside of the scope of this safety assessment.

Clinical guidelines

Therapeutic Guidelines

Clinical guidelines are provided for the treatment of delayed puberty or precocious puberty. External links to other resources are provided on the site for trans- and gender diverse health¹³.

The Royal Children’s Hospital Melbourne – Australian standards of care and treatment guidelines for trans and gender diverse children and adolescents¹⁴ provides broad clinical guidance and advice with a section on ‘*Puberty suppression*’. In relation to safety, the main concern outlined in this document is the impact of puberty suppression on bone mineral density ‘*due to the absence of effect of oestrogen or testosterone on bone mineralisation during this time*’, and that ‘*the long term impact of puberty suppression on bone mineralisation is currently unknown*’.

GnRH agonists listed for off-label use in this document are:

- Goserelin 10.8 mg subcutaneous implant

	<ul style="list-style-type: none"> Leuprorelin 22.5 mg or 30 mg intramuscular injection Triptorelin 22.5 mg intramuscular injection
Impact on Aboriginal and Torres Strait Islander Peoples	There were no reports in patients identifying as Aboriginal and/or Torres Strait Islander in AEMS; however, it is noted that for a majority of the reports, ethnicity has not been provided (46 of the 65 reports). The impact of intersectionality is likely to be significant for patients identifying as both Aboriginal and/or Torres Strait Islander and gender diverse. This must be considered in any future communication about this issue.
Impact on other priority populations	The safety of puberty blockers has an important impact on the gender diverse community. This should be taken into account in the event that further communication or regulatory action is required.
Discussion and conclusions	<p>Puberty blockers for use in children for gender-affirming care/gender dysphoria is not a registered indication in Australia, and is therefore considered as off-label use in this population.</p> <p>GnRH agonists are the class of medicines used as puberty blockers in Australia. Currently, GnRH products containing leuprorelin or triptorelin embonate are registered for the treatment of CPP in children aged 2 years and over under the close supervision of a paediatric endocrinologist, paediatrician or endocrinologist with experience in managing CPP.</p> <p>Safety information regarding use in children is largely similar across products registered for CPP and is also in line with international labels. In addition, none of the GnRH agonists are registered in these overseas countries for use in gender-affirming care/gender dysphoria.</p> <p>A search of AEMS did not identify reports related to use of GnRH agonists for the treatment of gender-affirming care/dysphoria. No specific signal (drug-adverse event pair) has been detected in this safety assessment. Published literature was identified in relation to puberty suppression in children and adolescents in gender-affirming care/dysphoria. Further review of this literature may be considered if a signal is detected in future; however, for the purposes of post-market medicines safety surveillance and regulation, a full literature review is not warranted at this stage.</p>
Recommendations and proposed action.	<p>Recommendations:</p> <p>Return to routine monitoring.</p>

References:

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From: s 22
To: s 22
Subject: FW: Advice on safety of puberty blockers [SEC=OFFICIAL]
Date: Wednesday, 29 January 2025 4:21:09 PM
Attachments: [image001.png](#)
[MB24-000896.docx](#)

Hi s 22

Here are the talking points we put together, and the attached brief is on a similar issue, just in case it helps with your SAP,

Many thanks,

s 22

From: s 22 @health.gov.au>
Sent: Thursday, 23 January 2025 9:27 PM
To: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Cc: s 22 @health.gov.au>; s 22 @health.gov.au>;
s 22 @health.gov.au>
Subject: Advice on safety of puberty blockers [SEC=OFFICIAL]

Hi Nick,

Talking points as discussed. A huge thanks to s 22 for pulling these together!

Medicines for gender-affirming care

- Medicines referred to as 'puberty blockers' are gonadotrophin-releasing hormone analogues (GnRHAs).
- In Australia, GNRHAs have only been indicated for use by the Therapeutic Goods Administration (TGA), and are only available on the Pharmaceutical Benefits Scheme (PBS), for the treatment of certain cancers and precocious puberty.
- There are five single ingredient, and two combination product GnRHAs currently registered on the Australian Register of Therapeutic Goods (ARTG): leuprorelin acetate, triptorelin acetate, goserelin acetate, nafarelin acetate, and triptorelin embonate; goserelin/bicalutamide and leuprorelin/bicalutamide.
- Of these products, only leuprorelin and triptorelin are registered for use in children (for the treatment of central precocious puberty (CPP)).
- The efficacy and safety of GNRHAs in gender-affirming care has not been assessed by the TGA as the TGA has not approved GNRHAs for this indication.
- When these medicines are prescribed in Australia for gender-affirming care, they are prescribed off-label using private prescriptions.

Safety monitoring

- Leuprorelin and Triptorelin contain safety information in their Product Information (PI) documents regarding use in children for CPP, including:
 - Special warning and precautions for use for idiopathic intracranial hypertension, convulsions, and changes in bone mineral density.
 - Information about more common adverse events such as injection site reactions

and gastrointestinal symptoms.

- The TGA has received 2223 reports of adverse events associated with GnRHAs. Of these reports, 64 were reported in children and adolescents (with most reports in children under 10 years):
 - 44 of these were classified as serious (many of these were related to severe injection site reactions).
 - There were no fatal cases.
- The TGA assessed the signal of GnRHAs and intracranial hypertension in September 2024 and determined that the information in the PI documents adequately described the risks.

Options for monitoring the safety of medicines used for off-label indications

- The TGA **could** conduct a safety signal analysis for the serious paediatric adverse events captured by our database for these products.
- This review would be limited because:
 - Most of the available clinical evidence is likely to be from international populations (where clinical practice guidelines differ) and not generalisable to the Australian public.
 - Most of the available clinical evidence is likely to be for approved indications (and therefore in pre-adolescents).
 - It is not possible to assess the risk-benefit profile in the absence of efficacy data.
 - It is not possible to calculate rates of adverse events for this indication as we do not have usage information from off-label prescriptions.

Background

- The TGA approves and regulates therapeutic goods based on the determination that the benefits of each therapeutic good outweigh the risks for its intended use (indication).
- The process of determining that the benefits of a medicine for a particular indication outweigh the risks requires a sponsor to apply to register a new medicine, or a new indication for an existing medicine.
- Once a medicine is registered on the ARTG, the TGA has robust pharmacovigilance processes in place to monitor safety. When investigations identify new safety information, the TGA takes prompt regulatory action.
- The TGA does not regulate how a medicine is used in clinical practice.
- 'Off-label' use refers to the use of a registered medicine for an indication or intended purpose other than those approved by the TGA. The efficacy and safety of a medicine for an 'off-label' indication has not been assessed by the TGA and the TGA cannot determine whether the benefits outweigh the risks for that particular indication.
- Sponsors are required to report adverse events to the TGA regardless of whether the medicine was used for an approved or unapproved indication. However, many adverse event reports do not specify the indication for which the medicine was used.
- If there is a safety concern regarding off-label use of a medicine, the TGA can assess the available clinical evidence to support or refute a potential link between a medicine and an identified safety problem or adverse event. This will include a literature review, search of the TGA's adverse event database, the international World Health Organisation (WHO) adverse event database (VigiBase) and review of the actions of comparable overseas regulators.
- If the TGA confirms a new safety concern that is associated with off-label prescribing,

regulatory action may be taken to ensure that the PI document clearly communicates the risks and accurately characterises the known safety profile of the medicine.

- Regulatory options that are available for approved indications, such as suspension and cancellation, are not applicable to off-label use.
- While off-label use of medicines is not illegal, it should always be in the setting of informed consent with consideration of the risks and benefits for that individual patient. This is a clinical practice matter between the doctor and their patient.

There is a recent ministerial brief on the CASS review and its relevance in the Australian context – MB24-000896 (attached for reference).

Thanks,

s 22

s 22

A/g Principal Medical Adviser – Pharmacovigilance Branch

Please note that my working days are Monday, Tuesday and Thursday

Making flexibility work - if you receive an email from me outside of normal business hours please do not feel compelled to respond. Unless I reach out to you via phone, I am not expecting you to read or reply until normal business hours.

Medicines Regulation Division | Health Products Regulation Group
Pharmacovigilance Branch

Australian Government Department of Health and Aged Care

E: s 22 @health.gov.au

P: s 22

PO Box 100, Canberra ACT 2601

This email comes to you from Ngunnawal Country. The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

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From: s 22
To: s 22
Cc: [Signal Investigation Coordinator](#)
Subject: New SAP based on EMA notification [SEC=OFFICIAL]
Date: Wednesday, 29 January 2025 2:04:00 PM
Attachments: [image001.png](#)

Hi s 22

We have been asked to complete a high priority SAP following the EMA's recent ban of puberty blockers: <https://www.gov.uk/government/news/ban-on-puberty-blockers-to-be-made-indefinite-on-experts-advice>

Would you mind taking this on? The signal folder is here: [E25-41923](#) and I'll talk to you more about it at our catch up this afternoon

Thanks so much,

s 22

Dr s 22
s 47E(e), s 47F - Medicines Surveillance and Signal Investigation
Pharmacovigilance Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health

E: s 22

Ph: s 22

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present

From: s 22
To: [Signal Investigation Coordinator](#)
Subject: FW: Advice on safety of puberty blockers [SEC=OFFICIAL]
Date: Friday, 24 January 2025 12:07:46 PM
Attachments: [image001.png](#)

Hi SCU,

Would you mind creating a new signal folder for 'safety of puberty blockers' and adding to our evaluation queue? This has come from exec so not a traditional drug-AE pair.

Thanks so much,

s 22

From: s 22
Sent: Friday, 24 January 2025 11:53 AM
To: s 22
Cc: s 22
Subject: FW: Advice on safety of puberty blockers [SEC=OFFICIAL]

Hi s 22

Thank you for all your work last night – Tony again today said how impressed he was with your talking points, pulled together at such short notice.

Just wanted to let you know what was discussed today:

- The Ministers Office advised that NMHRC are pulling together a proposal (to submit likely late next week) for an 18-month project for this issue. This will likely start with a review of the available evidence before development of clinical guidelines.
- The TGA have a meeting on Wednesday next week with the NMHRC to determine what information we could feed into this from a pharmacovigilance perspective. Likely it will be a safety analysis of the AE reports in our database for people under 18 years – noting the limitations we discussed yesterday (and will flag at the meeting with NHMRC). This analysis will at the very least need to include a literature review, concerted effort to obtain information from international regulators, and potentially utilise ACM.

Please could you set up a meeting with s 22 and I for Tuesday to discuss further? My diary is very tight but I could do straight after s 22 meeting?

Many thanks,

s 22

From: s 22
Sent: Friday, 24 January 2025 11:37 AM
To: s 47E(c), s 47F @Health.gov.au>
Cc: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Subject: Advice on safety of puberty blockers [SEC=OFFICIAL]

Dear s 47E(c), s 47F

It was lovely to meet you today. Please find below some information to supplement our discussion this morning.

Background

- The TGA approves and regulates therapeutic goods based on the determination that the benefits of each therapeutic good outweigh the risks for its intended use (indication).
- The process of determining that the benefits of a medicine for a particular indication outweigh the risks requires a sponsor to apply to register a new medicine, or a new

indication for an existing medicine.

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 - There were no fatal cases.
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We look forward to meeting with the NHMRC next week.

Please do not hesitate to reach out if you have any questions.

Many thanks,

s22

s 22

A/g Principal Medical Adviser – Pharmacovigilance Branch

Please note that my working days are Monday, Tuesday and Thursday

Making flexibility work - if you receive an email from me outside of normal business hours please do not feel compelled to respond. Unless I reach out to you via phone, I am not expecting you to read or reply until normal business hours.

Medicines Regulation Division | Health Products Regulation Group

Pharmacovigilance Branch

Australian Government Department of Health and Aged Care

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