EUROPEAN MEDICINES AGENCY
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Pharmacovigilance and Epidemiology Department

Cyproterone-containing medicines and Meningiomas

EudraVigilance analysis

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1. Abbreviations

ADR	Adverse drug reaction
EEA	European Economic Area
EMA	European Medicines Agency
EV	EudraVigilance
EVDAS	EudraVigilance Data Analysis System
HLGT	High level group term
HLT	High level term
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCA	National competent authority
PT	Preferred term
SMQ	Standardised MedDRA Query
SOC	System organ class

2. Roles and responsibilities

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Sign-off	Peter Arlett

3. Administrative information

Type of procedure	Referral
Procedure number	EMEA/H/A-31/1488

4. Milestones

Milestone	Planned	Actual
Data analysis plan	August 2019	August 2019
Internal report	2 September 2019	26 September 2019
Peer-review	5 September 2019	27 September 2019
Implementation of corrections	12 September 2019	04 October 2019

5. Background

In the context of the referral procedure EMEA/H/A-31/1488, the PRAC has requested an analysis of EV data on meningiomas related to cyproterone-containing medicines.

According to National Cancer Institute, meningioma is a primary central nervous system (CNS) tumour. Overall, meningiomas are the most common type of primary brain tumour. However, higher grade meningiomas are very rare. Meningiomas are more common in females, but grades II (atypical meningiomas, mid-grade tumours) and III (malignant) occur more often in males. They are most common in black people, followed by white people, and then Asian-Pacific Islanders. The meningiomas tend to occur in people around 60 years old, with the risk increasing with age.

Meningiomas form along the dura mater, the outermost layer of tissue that covers and protects the brain and spinal cord. The dura mater is one of three layers that form the meninges. Meningiomas arise from meningeal cells. As a result, they tend to occur along the surface of the brain. Meningiomas can spread to other areas of the CNS through cerebrospinal fluid (CSF). Grade II meningiomas can invade surrounding tissue, including nearby bone tissue. Grade III meningiomas have irregular cells and are likely to invade the brain or spread to other organs in the body.

Symptoms related to a meningioma depend on the tumour's location. People with a meningioma may have vision changes, loss of hearing or smell, confusion, seizures, or headaches.

6. Aims

The primary objective of the EudraVigilance analysis was:

- To identify and describe case reports to cyproterone-containing medicinal products;
- To identify and characterise case reports to these products where meningiomas were also reported.

7. Methods

7.1. Database

The database used was EudraVigilance. The period of interest is from start of data collection (i.e. 1995) to 28 August 2019.

7.2. Ontology

The Medical Dictionary for Drug Regulatory Activities (MedDRA) v.21.1 was used to code the outcomes of interest and extract the data.

7.3. Exposure

The exposure was defined as the use of medicinal products containing cyproterone alone and in combination with ethinylestradiol or estradiol valerate.

The characterisation of drug role [ICH E2B(R3) G.k.1] included suspect, interacting and concomitant.

7.4. Case definition

A case of meningioma was defined as a report with at least one MedDRA term of the following:

- Anaplastic meningioma
- Intracranial meningioma malignant
- Intraosseous meningioma
- Malignant meningioma metastatic
- Meningioma
- Meningioma benign
- Meningioma malignant
- Meningioma surgery
- Spinal meningioma benign
- Spinal meningioma malignant
- Meningeal neoplasm
- Metastases to meninges

7.5. Covariates

The covariates considered where age, gender, indication for use, time-to-onset, outcome, country of origin and reporter's qualification.

7.6. Analytical plan

Descriptive statistics were performed by age, gender, indication for use, route of administration and origin of reports for all case reports. Where feasible, boxplots of age and time to onset were plotted.

8. Results

8.1. Overview

There were 871 (10%) case reports of meningioma cases (see case definition) to cyproterone-containing medicinal products out of a total of 8678 case reports (Table 1).

The vast majority of these reports are to cyproterone as single ingredient coded with Androcur brand and associated generic product, and are non-fatal. Of the forty nine cases reported with the brand name Diane (incl. Diane 35 or Mite), only 12 do not list Androcur (or associated names) as a co-suspect medication. Of the seven cases reported with brand name Climene, only two do not list Androcur as co-suspect medication (refer to Annex table 1). Only eleven of these cases are not from the EEA and are reported by physicians mostly (377) followed by consumer or non-healthcare professionals (326).

Of the total 871 meningioma cases, in those cases with reported history in structured fields, 25 had meningioma, 10 radiotherapy, 17 androgenetic alopecia and four 21-hydrolase deficiency (not shown in table 1).

Table 1: Overview of case reports to cyproterone-containing medicinal products stratified by characteristics

Characteristics	Meningioma case	Other adverse reactions	Total
N	871	7807	8678
Age group *N (%)*[a]			

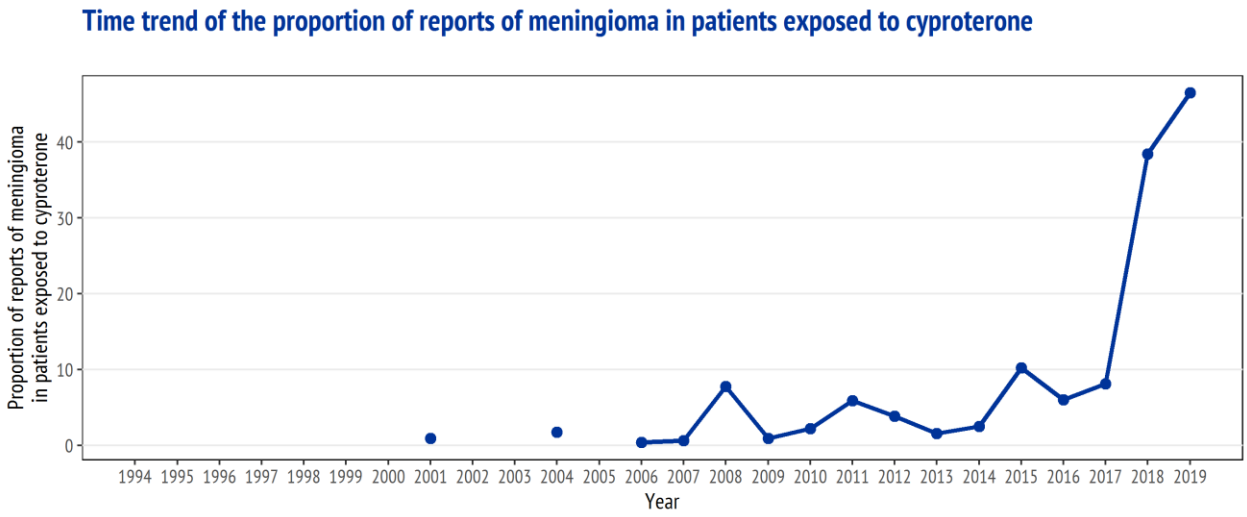
Characteristics	Meningioma case	Other adverse reactions	Total
0 to 25	2 (0.7)	1741 (33.8)	1743 (32.1)
25 to 44	106 (39.0)	2140 (41.5)	2246 (41.4)
45 to 64	142 (52.2)	583 (11.3)	725 (13.4)
65 to 74	15 (5.5)	317 (6.1)	332 (6.1)
75 and older	7 (2.6)	376 (7.3)	383 (7.1)
Gender *N (%)*[a]			
Female	806 (93.2)	6179 (80.6)	6985 (81.9)
Male	59 (6.8)	1483 (19.4)	1542 (18.1)
Substance *N*[ab]			
Cyproterone	857 (93.4)	2250 (28.3)	3106 (35.1)
Cyproterone acetate, estradiol valerate	7 (0.8)	372 (4.7)	374 (4.2)
Cyproterone, ethinylestradiol	53 (5.8)	5321 (67.0)	5374 (60.7)
Drug role *N (%)*[ac]			
Concomitant	12 (1.3)	2565 (32.3)	2577 (29.1)
Suspect	905 (98.7)	5330 (67.1)	6235 (70.3)
Interacting	0 (0.0)	54 (0.7)	54 (0.7)
Outcome *N (%)*[a]			
Fatal	3 (0.3)	429 (5.5)	432 (5.0)
Non fatal	868 (99.7)	7378 (94.5)	8246 (95.0)
Origin *N (%)*[a]			
European Economic Area	860 (98.7)	5384 (69.0)	6244 (72.0)
Non European Economic Area	11 (1.3)	2301 (29.5)	2312 (26.6)
Not Specified	0 (0.0)	122 (1.6)	122 (1.4)
Reporter qualification[d] *N (%)*[a]			
Physician	377 (43.3)	2760 (36.0)	3137 (36.8)
Consumer or other Non-Health Professional	326 (37.5)	2464 (32.2)	2790 (32.7)
Other health professional	33 (3.8)	707 (9.2)	740 (8.7)
Pharmacist	33 (3.8)	671 (8.8)	704 (8.3)
Consumer or other Non-Health Professional, Physician	19 (2.2)	427 (5.6)	446 (5.2)
Other health professional, Physician	22 (2.5)	227 (3.0)	249 (2.9)
Consumer or other Non-Health Professional, Other health professional	11 (1.3)	148 (1.9)	159 (1.9)
Consumer or other Non-Health Professional, Lawyer	31 (3.6)	17 (0.2)	48 (0.6)
Consumer or other Non-Health Professional, Lawyer, Physician	10 (1.1)	9 (0.1)	19 (0.2)
MedDRA Neoplasm SOC reported reaction *N (%)*[a]			
No	1 (0.1)[e]	7423 (95.1)	7424 (85.5)
Yes	870 (99.9)	384 (4.9)	1254 (14.5)
Medical history *N (%)*[f]			
History or indication for malignancy	89 (10.2)	1081 (13.8)	1170 (13.5)
History of diabetes	23 (2.6)	168 (2.2)	191 (2.2)
History of radiotherapy	8 (0.9)	67 (0.9)	75 (0.9)
History of neurological congenital malformations	0 (0.0)	8 (0.1)	8 (0.1)

[a] Column-wise proportion (i.e. proportion within the characteristic)
[b] Cases may have more than one substance reported
[c] Cases with more than one substance may report multiple drug roles
[d] Showing only qualifications reported at least ten times in meningioma cases
[e] One case of meningioma surgery is counted as meningioma case, but formally is not part of the Neoplasms SOC in MedDRA
[f] Row-wise proportion (i.e. proportion of total counts)

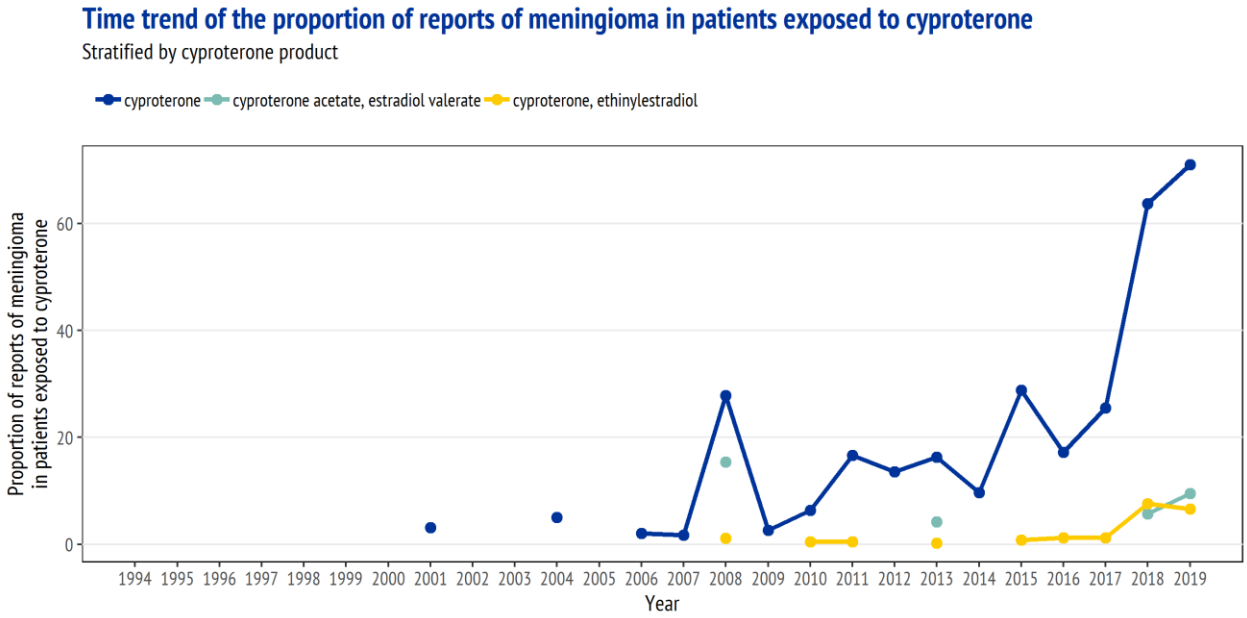
8.2. Meningiomas

8.2.1. Time trends

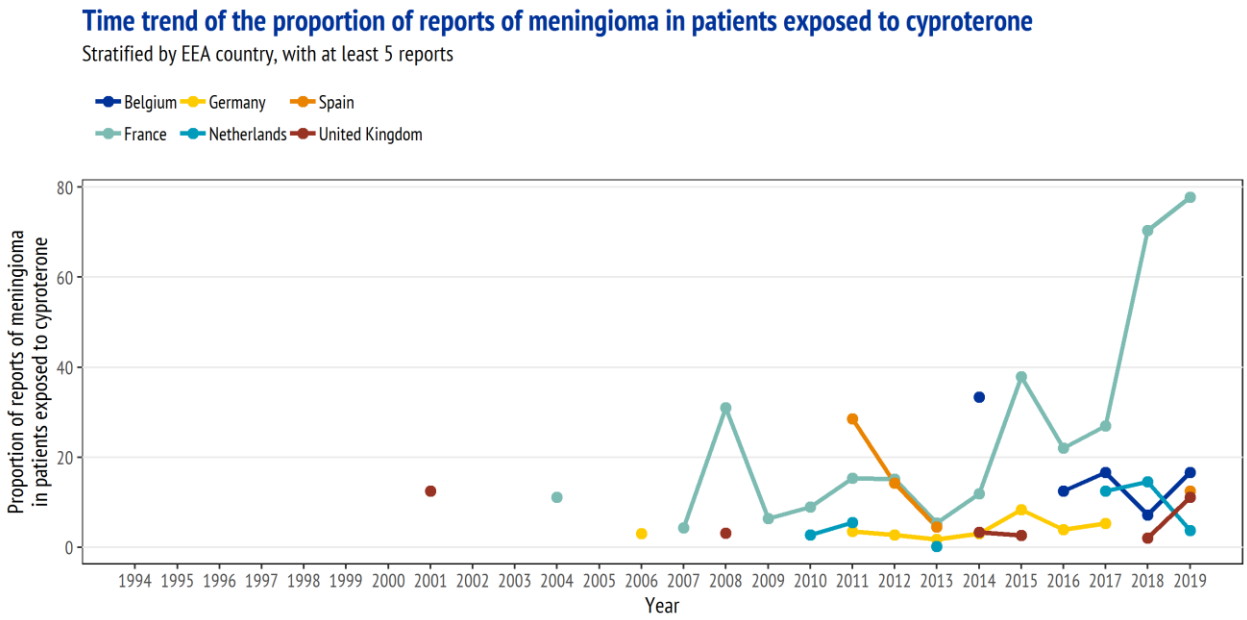
The time trend of the proportion of reports of meningioma in patients exposed to cyproterone indicates that a peak reporting occurred in 2017-2019, before that, the proportion was 10% or lower, but rose to around 40-45%, a four-fold increase.



As noted in Table 1, most reports seem to be to the single ingredient cyproterone formulations. In fact, for these products, the proportion of reports of meningioma in the past two years has exceeded 60%.

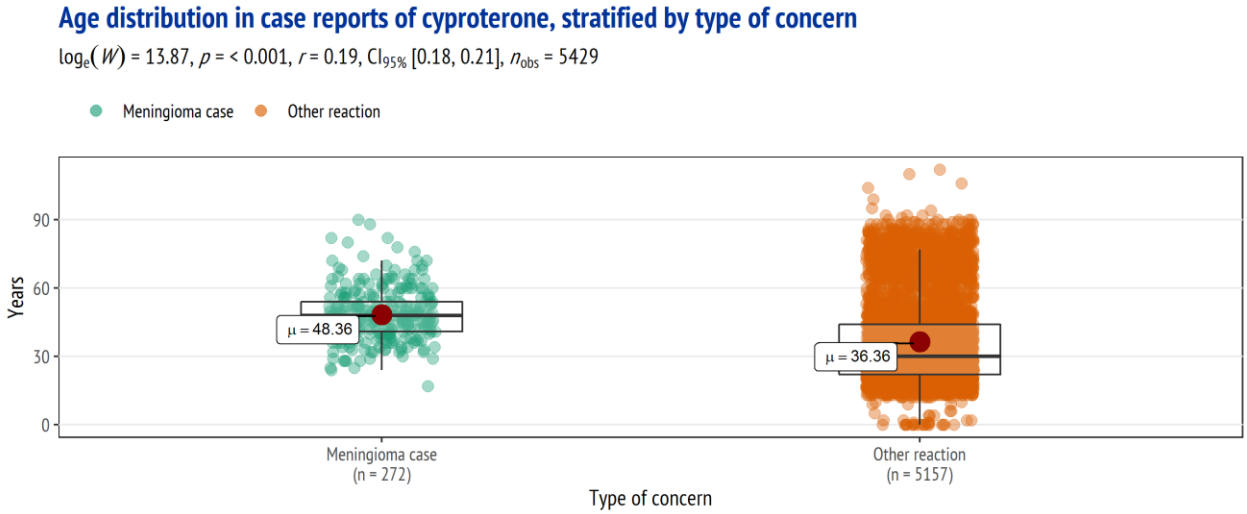


Stratifying the trend by EEA country, it becomes evident that the main drivers of this increase are case reports from France.



8.2.2. Demographics

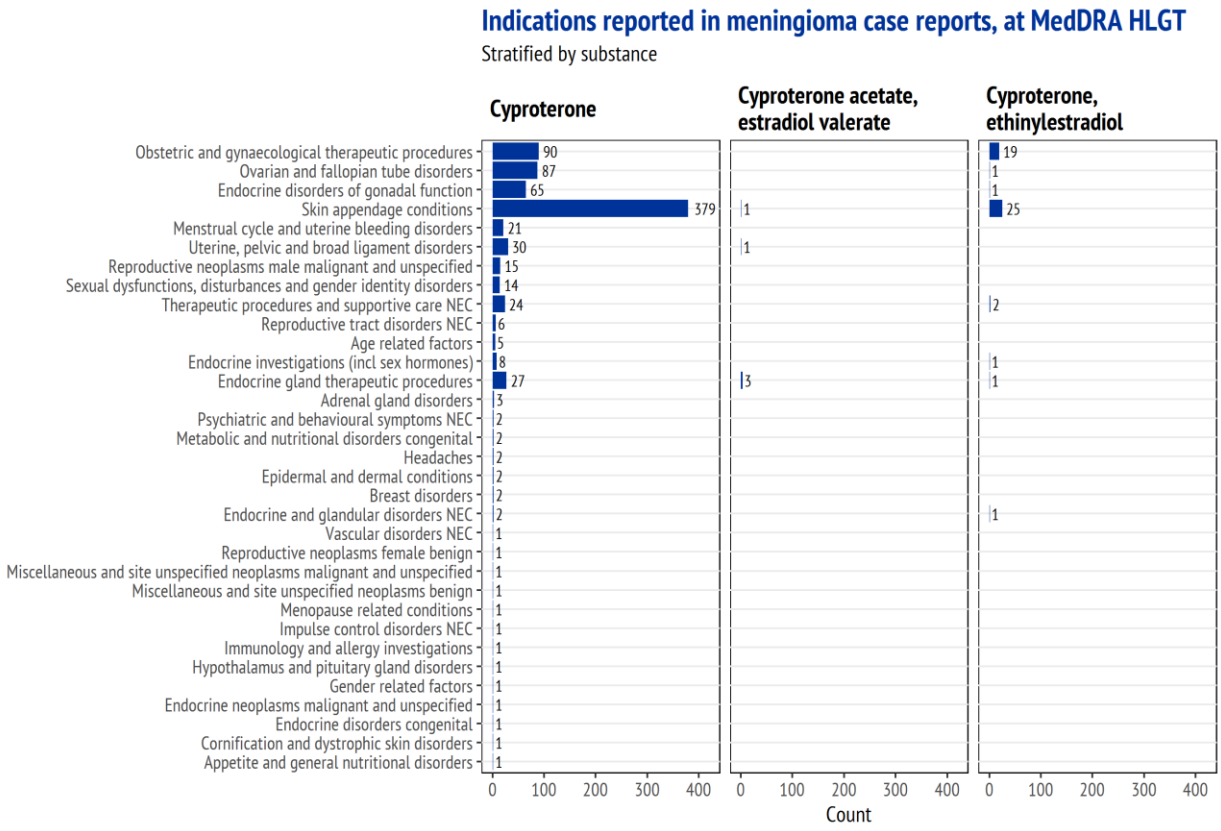
The mean age of patients who had meningioma was statistically significantly higher than the mean age of patients having any other adverse drug reaction ($mean_{meningioma}$ = 48 vs. $mean_{other}$ = 36).



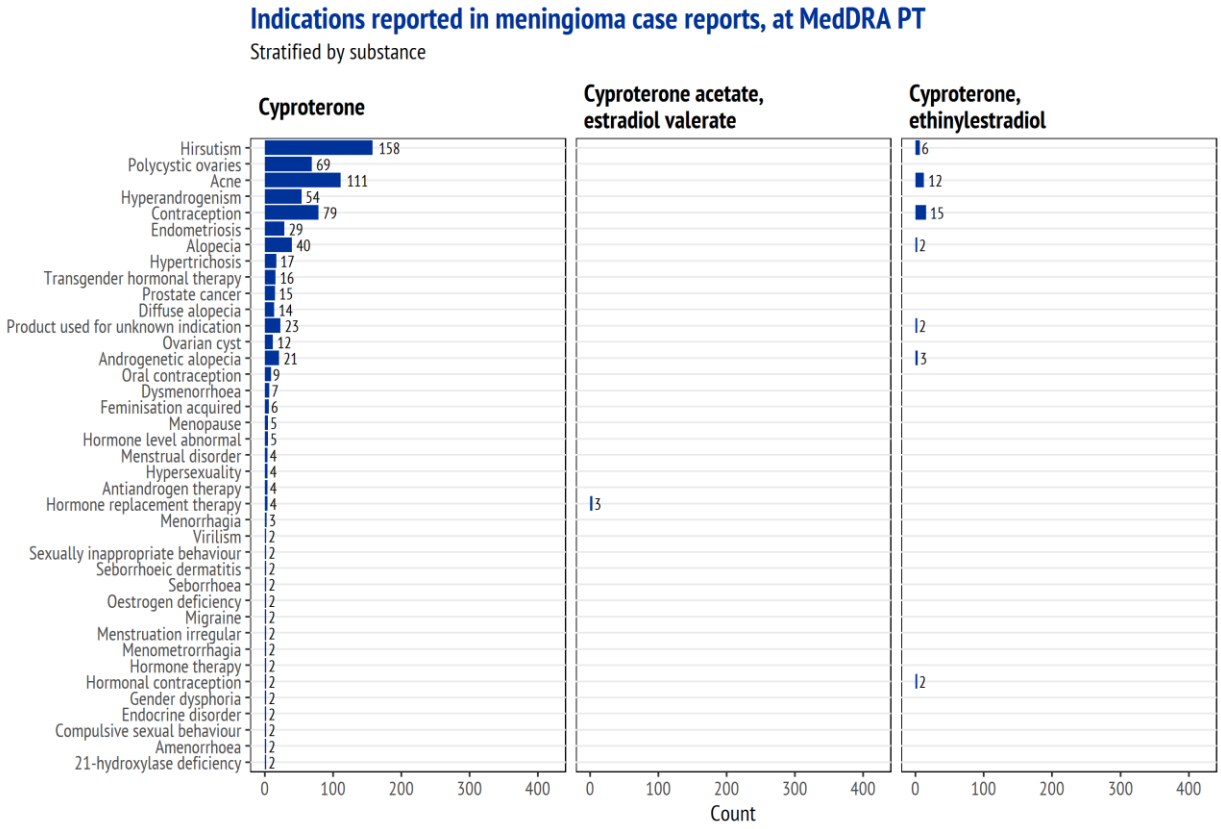
Vast majority of cases, 806, referred to female patients. Fifty nine (59) meningioma cases sent with male gender refer mainly to treatments of prostate cancer and transgender hormonal therapy (refer to table 2 in Annex for EV literature cases). In six (6) cases gender was not specified.

8.2.3. Indications for use

Cyproterone-containing medicinal products were mostly used for skin appendage conditions, followed by obstetric and gynaecological therapeutic procedures and ovarian and fallopian tube disorders. Note that a case report may have more than one indication reported.

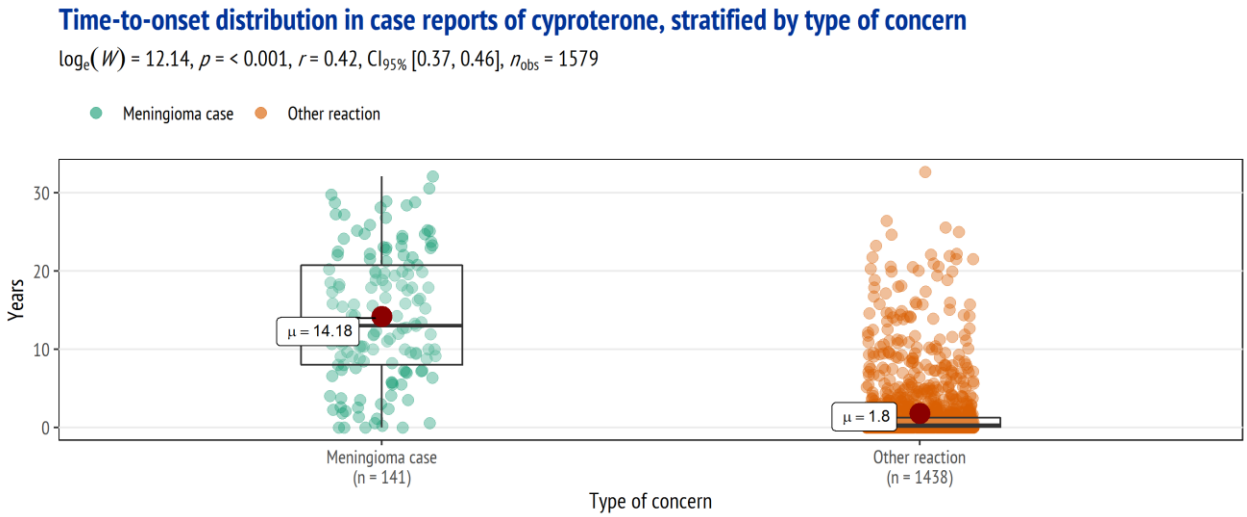


A more granular look at the indications reveals that hirsutism and acne were the most common reported uses of cyproterone-containing medicinal products.

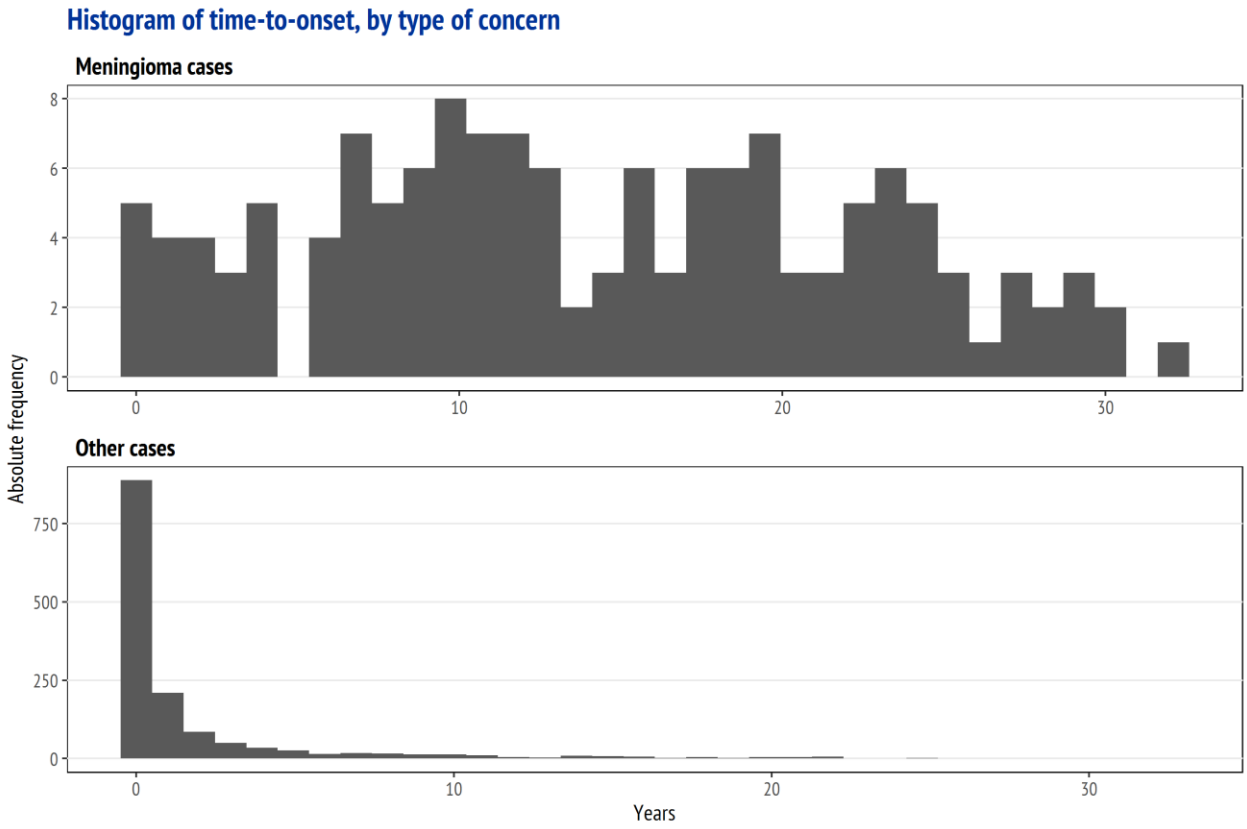


8.2.4. Time-to-onset

The mean time-to-onset of meningioma cases was 14 years, with an interquartile range between 8 and 20 years. While extremely variable, the Wilcoxon test suggests a statistically significant difference to all other reactions, including other adverse reactions of malignancy.

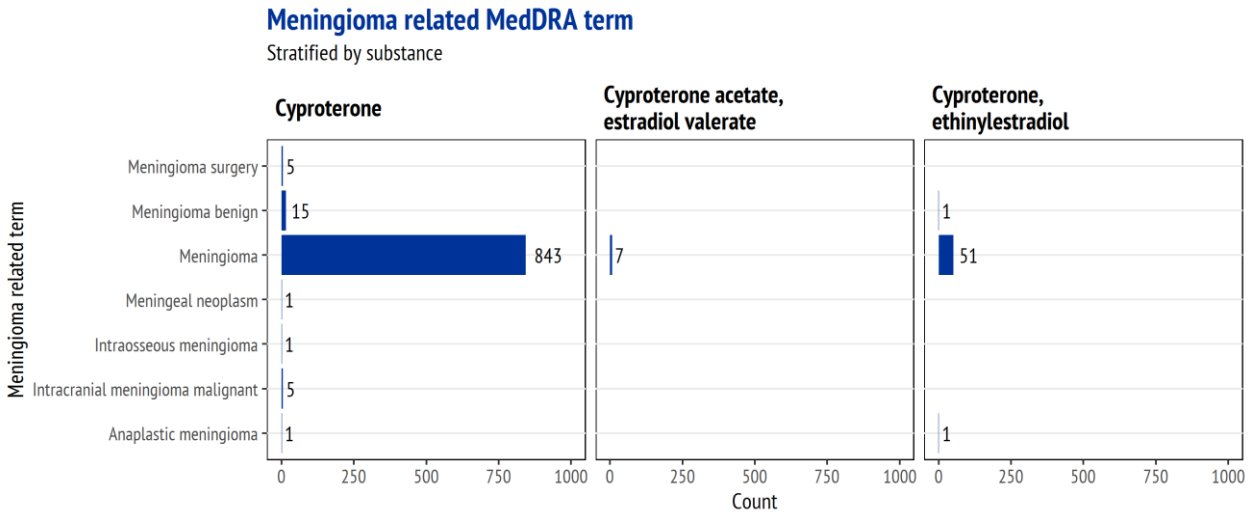


A detailed time to onset histogram in years is presented below with a consistent long onset after therapy start.



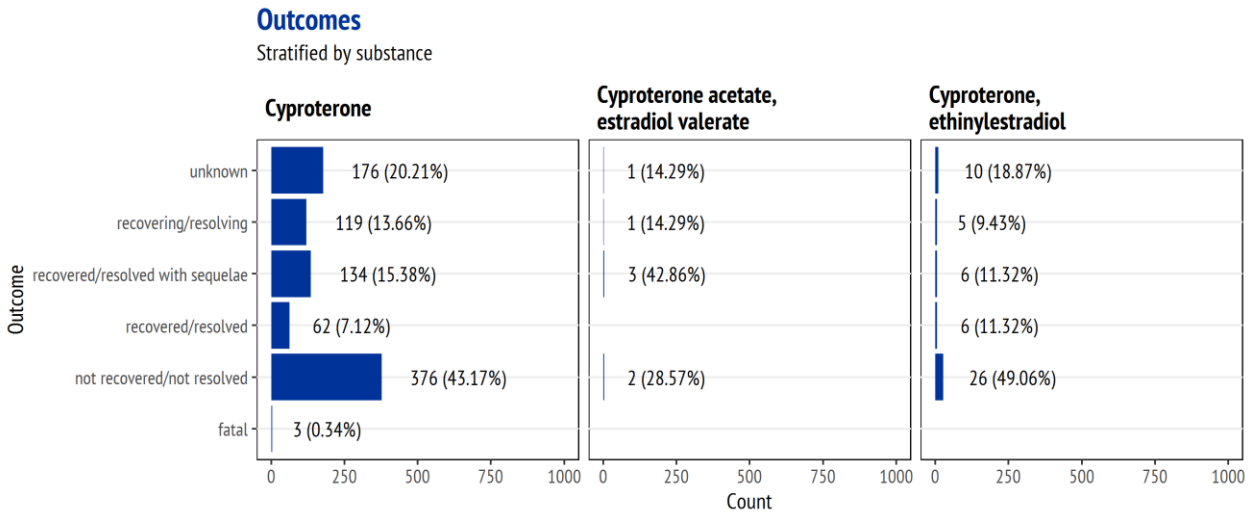
8.2.5. Reported reactions

The case definition of meningioma includes several different MedDRA PT. Of these, the meningioma PT is by far the most commonly reported for substances. Note that each case may have more than one PT reported.



8.2.6. Reported outcomes

The most commonly reported outcome was not recovered/not resolved. Three case reports, of patients taking the single ingredient cyproterone, were fatal.



9. Discussion

Over ten percent of all case reports to cyproterone are of meningiomas. However, 628 (72%) of these cases have been reported in 2018-2019. Furthermore, 606 of the case reports received in 2018 and 2019 stem from a single country, France.

Geographical and temporal clusters of case reports raise the possibility of reporting bias, due to media awareness, regulatory action or could reflect regional treatment regimens or preferences. One way to assess whether geographical and temporal clusters are due to biases is to profile the reaction start date: typically the receive date of a report is in short sequence to the reaction date – i.e. reporters report soon after noticing the suspected reaction. In this case, in 628 cases reported in 2018-2019, there were 634 reactions reported (some cases reported more than one reaction in the case definition). Of these, 340 reactions did not have a start date, 169 started in the period and 125 started the years before.

Hence, there is a hint of evidence that just under half of the cases that reported a reaction start date are historical, indicating a possible bias affecting the number of reports.

Reporting bias however, says little about the causality between a drug and a reaction. The demographics and the time-to-onset results seem to be reasonably consistent with a casual mechanism.

Radiation induced meningiomas[1] seem to have a time-to-onset of, on average, 13 years, this is extremely close to the mean time-to-onset in our analysis. Obviously, radiation and medication would have distinct mechanisms, and one would expect radiation to have a shorter time-to-onset as compared to medication, which it only slightly does in this study.

The strength of evidence that pharmacovigilance databases can provide for malignancy concerns is known to be limited. However, in this case, it can be cautiously asserted that the information collected does not contradict the presence of a potential causal role of cyproterone, particularly with long durations of use, and in fact shows patterns consistent with other known causes of meningiomas.

[1] Yamanaka R, Hayano A, Kanayama T. Radiation-Induced Meningiomas: An Exhaustive Review of the Literature. World Neurosurg. 2017 Jan;97:635-644.e8. doi:10.1016/j.wneu.2016.09.094. Epub 2016 Oct 3. Review. PubMed PMID: 27713063.

Annex:

Cyproterone-containing medicinal product reported to EV

Recoded Medicinal Product (High Level) and cases reported	
ACETATE DE CYPROTERONE ARROW	3
ACETATE DE CYPROTERONE SANDOZ	1
ACETATE DE CYPROTERONE SANDOZ 100 MG, COMPRIMÉ SÉCABLE	1
ACETATE DE CYPROTERONE TEVA	1
ACETATE DE CYPROTERONE TEVA TEVA	1
ANDROCUR	768
ANDROCUR DEPOT	2
CLIMENE	7
CYPRONE	1
CYPROTERONACETAT BETA	1
CYPROTERONE	80
CYPROTERONE BIOGARAN	7
CYPROTERONE MYLAN	2
CYPROTERONE, ETHINYLESTRADIOL	3
CYPROTERONE/ETHINYLESTRADIOL TEVA	1
DIANE	37
DIANE 35	10
DIANE MITE	1
DIANE-35	1

Table 2: EV literature cases

No	Reference
1.	Zairi F, Aboukais R, Rhun EL, Marinho P, Maurage CA, Lejeune JP. Close follow-up after discontinuation of cyproterone acetate: a possible option to defer surgery in patients with voluminous intracranial meningioma. JOURNAL OF NEUROSURGICAL SCIENCES. 2017;61 (1):97-101
2.	A. L. Bernat, K. Oyama, S. Hamdi, E. Mandonnet, D. Vexiau, M. Pocard, B. George, S. Froelich. Growth stabilization and regression of meningiomas after discontinuation of cyproterone acetate: a case series of 12 patients. Acta Neurochir. 2015;157:1741-1746
3.	Alalade AF, Millward C, Pal P, Gilkes C. Multiple skull base meningiomata in a transgender patient: Case report and literature review. J-Neurol-Surg-B-Skull-Base 201;890:
4.	Alderman CP. Probable drug-related meningioma detected during the course of medication review services. Consultant Pharmacist. 2016;31(9):500-504.
5.	BOTELLA C, COLL G, LEMAIRE JJ, IRTHUM B. Intra cranial meningiomas and long term use of cyproterone acetate with a conventional dose in women. A report of two cases of tumor decrease after treatment withdrawal.. Neurochirurgie. 2015;61(5):339-342
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7.	Bergoglio MT, Sola Izquierdo E, Veses Martin S, Hernandez Mijares A. Acute severe hyponatremia induced by aceclofen in a male patient with central diabetes insipidus. Endocrinologia y Nutricion. 2013;60 (6):338-40
8.	Bernat AL, Oyama K, Hamdi S, Mandonnet E, Vexiau D, Pocard M, et al. Growth stabilization and regression of meningiomasafter discontinuation of cyproterone acetate: a case series of 12 patients. Acta Neurochir. 2015;157:1741-6. DOI: 10.1007/s00701-015-2532-3. Accessed 2015 Aug 12.
9.	Bernat AL, Bonnin S, Labidi M, Aldahak N, Bresson D, Bouazza S, Froelich S. Regression of Giant Olfactory Groove Meningioma and Complete Visual Acuity Recovery after Discontinuation of Cyproterone Acetate. Journal of Ophthalmic and Vision Research. 2019;13:3:355-358
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13.	Chavant F, et al. Meningioma possibly induced by cyproterone acetate: About a new case report.. Fundamental and Clinical Pharmacology. 2016
14.	Cheserem J,Zebian B,Macdonald M,Hardwidge C. Regression of multiple meningiomata after cessation of cyproterone acetate treatment.. Journal of Neurological Surgery, Part B: Skull Base 2012 Jun;73(2):.
15.	El Rahal A; Eddy C; May A; Schaller K; Murek M. Abrupt regression of multiple meningiomas after discontinuation of cyproterone acetate (CPA) treatment: a case report and literature review. 17th European Congress of Neurosurgery: Controversies and Solutions in Neurosurg. 2017;Abstr:EP398
16.	Engelhardt J, Namaki H. Contralateral Transcranial Approach to Tuberculum Sellae Meningiomas: Long-Term. WORLD NEUROSURGERY. 2018;116:1066-074.
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18.	Froelich S, Dali-Youceif N, Boyer P, Kehrti P, Maitrot D, Auwerx J, Schlienger J-L Does cyproterone acetate promote multiple meningiomas? Endocrine abstracts 2008 16 158
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31.	S. de Graaff MSc, dr. M.D.A Lambers, drs. I.K. Haitsma, drs. M. Bandell. Het ontstaan van een meningeoom tijdens het gebruik van cyproteronacetaat. Nederlands Tijdschrift voor Obstetrie & Gynaecologie. 2018;131:248-250
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38.	Goncalves AMG, Page P, Domigo V, Meder JF, Oppenheim C. Abrupt regression of a meningioma after discontinuation of cyproterone treatment. Endothelium: Journal of Endothelial Cell Research. 2010; 31; 1504-1505
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