EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Inspection and Human Medicines Pharmacovigilance Division

Leuprorelin and medication error and lack of effect

An analysis of EudraVigilance

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1. Abbreviations

ADR	Adverse drug reaction
EEA	European Economic Area
HLGT	High level group term
HLT	High level term
LE	Lack of effect
ME	Medication error
MedDRA	Medical dictionary for drug regulatory activities
NEC	Not elsewhere classified
ROR	Reporting odds ratio
SMQ	Standardised MedDRA Query
SOC	System organ class

2. Roles and responsibilities

Analyst – Luis Pinheiro

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Sign-off – Xavier Kurz

3. Background

Leuprorelin is a gonadotropin releasing hormone (GnRH) agonist, which when used continuously leads to a decrease of gonadotrophin and sex steroid levels.

It is authorised in EU for the treatment of advanced hormone-dependent prostate cancer, breast cancer, endometriosis, symptomatic uterus myomatosus, uterine fibrosis, and precocious puberty.

Leuprorelin-containing depot products have duration of action of 1, 3 or 6 months. The product presentations include implants as well as powders and solvents for the preparation of injections. Leuprorelin-containing products are injected subcutaneously or intramuscularly.

There have been reports for medication errors possibly leading to lack of effect with all leuprorelin containg products. For one product (Eligard) there have been 2,271 cases of handling errors reported for the period from 1 January 2012 to 31 December 2018. In 120 cases, lack of effect associated with handling errors were reported.

As a consequence, on 7 June 2019, Germany notified PRAC about a referral under Article 31 of Directive 2001/83/EC for leuprorelin-containing products depot formulations in order to further characterise and mitigate the risk of handling errors and associated risk of lack of effect of leuprorelin-containing depot-injections.

In addition, the PRAC considered it necessary to perform a EudraVigilance analysis of reports of cases of medication errors with leuprorelin-containing products depot formulations. The data to perform this analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs. This EudraVigilance analysis will be provided to all MAHs together with the preliminary assessment reports.

4. Aims

The objective of this analysis was to describe the characteristics of reports of medication errors and lack of effect to leuprorelin.

5. Methods

5.1. Case definition

5.1.1. Concerns of interests

As the overarching concern is medication errors possibly leading to lack of effect, a composite case definition was used.

Cases of interest were considered to be all cases that have MedDRA preferred terms from any of the following: Lack of efficacy/effect SMQ (narrow), Product Issues SOC, Medication error SMQ (broad) and Reproductive hormone analyses HLT.

For simplicity, Lack of efficacy/effect will be referred from hereon as Lack of effect.

5.1.2. Absence of harm

To determine those case reports that have medication error, product issues, lack of effect or reproductive hormone analyses reported but for which no harm was reported, either because the medication error was intercepted (i.e. quasi-incident) or because the no harm occurred despite the error, two approaches were used.

On one hand, a list of terms that suggest that no harm occurred was used (see Appendix I). On the other hand, reports with the concerns of interest but without any other term were also considered as reports without harm.

5.2. Data extraction

All case reports in EudraVigilance, including the post-marketing module and the clinical trial module, mentioning leuproreline, either as suspect or interacting substance, from start of recording to 27 July 2019 were extracted.

5.3. Analytics

Descriptive statistics were performed to characterise the reports. These included an overview of case reports by population and drug characteristics, time-trend of case reports and distribution of reported reactions.

Disproportionality statistics were calculated for at HLT level. To perform the calculation at HLT level, all HLTs under the SMQs and SOCs as well as the HLT Reproductive hormone analyses were used.

6. Results

6.1. Overview of case reports

There are 20,211 reports of leuprorelin-containing medicinal products in EudraVigilance, of which 17,709 (87.6%) are serious (Table 1).

For the concerns of interest, there are 1,707 reports, or 8% of the total reports for leuprorelin-containing medicinal products.

Within the concerns of interest, reports of lack of effect and of reproductive hormone analyses were the most frequently reported as serious with 82.9% and 80.5% respectively.

Table 1: Characteristics of the reports for all reactions to leuprorelin-containing medicinal products, stratified by seriousness.

Characteristic	Non-serious report	Serious report	Total
	n (%)		n
Total	2,502	17,709	20,211
Age group			
0 to 25	48 (12.7)	331 (87.3)	379
25 to 44	120 (12.8)	815 (87.2)	935
45 to 64	174 (14.3)	1041 (85.7)	1215
65 to 74	248 (13.3)	1620 (86.7)	1868
75 and older	255 (7.9)	2964 (92.1)	3219
Gender			
Female	904 (16.2)	4669 (83.8)	5573
Male	1568 (11.2)	12444 (88.8)	14012
Origin			
European Economic Area	2333 (32.5)	4837 (67.5)	7170
Non EEA	160 (1.2)	12856 (98.8)	13016
Not Specified	9 (36.0)	16 (64.0)	25
Concerns			
Lack of effect SMQ (narrow)	130 (17.1)	629 (82.9)	759
Product Issues SOC	178 (70.6)	74 (29.4)	252
Medication error SMQ (broad)	442 (51.1)	423 (48.9)	865
Reproductive hormone analyses HLT	38 (19.5)	157 (80.5)	195

6.2. Reports for the concerns of interest

For the reports with concerns of interest, stratified by year, it is clear that the concerns of interest have increased significantly over the period of 2018 to July 2019 (Table 2). The proportion of reporting per year peaked in 2018, for all concerns, with a total of 462 cases (some cases have more than one concern reported). This was particularly evident for reports for the Product issue SOC, where more than 50% of the reports for the 2012-2019 period were received in 2018.

Interestingly, the cases seem to be coming from the EEA, as this increase occurs in the same period as peak reporting from the EEA.

Also noteworthy, is that 114 reports of the 462 (24.7%) total count case for 2018 had absence of reactions (i.e. terms that excluded reactions or absence of other terms, not in the case definition).

Table 2: Characteristics of the reports of the concerns of interest to leuprorelin-containing medicinal products, stratified by period. Data for the year 2019 is only up to 27 July. Percentages are calculated row wise (per category).

Characteristic	Period							
	2012	2013	2014	2015	2016	2017	2018	2019[a]

Characteristic	Period							
	n (%)							
n	48 (2.8)	117 (6.9)	159 (9.3)	109 (6.4)	149 (8.7)	184 (10.8)	462 (27.1)	245 (14.4)
Age group								
0 to 25	0 (0.0)	3 (10.0)	4 (13.3)	0 (0.0)	2 (6.7)	3 (10.0)	8 (26.7)	10 (33.3)
25 to 44	2 (3.4)	5 (8.5)	3 (5.1)	2 (3.4)	11 (18.6)	7 (11.9)	19 (32.2)	10 (16.9)
45 to 64	6 (4.7)	15 (11.8)	14 (11.0)	10 (7.9)	9 (7.1)	20 (15.7)	32 (25.2)	21 (16.5)
65 to 74	4 (2.9)	7 (5.1)	16 (11.6)	9 (6.5)	14 (10.1)	22 (15.9)	45 (32.6)	21 (15.2)
75 and older	4 (2.7)	11 (7.4)	9 (6.0)	11 (7.4)	15 (10.1)	28 (18.8)	49 (32.9)	22 (14.8)
Gender								
Female	21 (4.4)	35 (7.4)	65 (13.7)	35 (7.4)	69 (14.6)	53 (11.2)	117 (24.7)	79 (16.7)
Male	27 (2.8)	73 (7.6)	89 (9.2)	72 (7.5)	80 (8.3)	128 (13.3)	335 (34.8)	159 (16.5)
Outcome								
Fatal	1 (2.0)	4 (8.2)	9 (18.4)	5 (10.2)	6 (12.2)	8 (16.3)	11 (22.4)	5 (10.2)
Origin								
EEA	18 (2.2)	34 (4.2)	67 (8.2)	47 (5.8)	56 (6.9)	89 (10.9)	334 (41.1)	168 (20.7)
Non-EEA	30 (4.5)	83 (12.6)	92 (13.9)	62 (9.4)	93 (14.1)	95 (14.4)	128 (19.4)	77 (11.7)
Concerns[b]								
LE SMQ	29 (4.8)	62 (10.4)	82 (13.7)	66 (11.0)	77 (12.9)	77 (12.9)	136 (22.7)	70 (11.7)
ME SMQ	15 (1.8)	55 (6.7)	64 (7.8)	39 (4.8)	71 (8.7)	100 (12.2)	312 (38.2)	161 (19.7)
PI SOC	4 (1.6)	4 (1.6)	18 (7.3)	10 (4.1)	15 (6.1)	20 (8.2)	128 (52.2)	46 (18.8)
RHA HLT	5 (3.3)	8 (5.3)	13 (8.6)	15 (9.9)	24 (15.9)	24 (15.9)	42 (27.8)	20 (13.2)
Seriousness type								
Death	1 (2.0)	4 (8.2)	9 (18.4)	5 (10.2)	6 (12.2)	8 (16.3)	11 (22.4)	5 (10.2)
Hospitalisation	10 (4.6)	29 (13.4)	31 (14.3)	30 (13.8)	29 (13.4)	33 (15.2)	33 (15.2)	22 (10.1)
Life threatening	3 (18.8)	0 (0.0)	3 (18.8)	2 (12.5)	1 (6.2)	2 (12.5)	4 (25.0)	1 (6.2)
Disabling	2 (8.7)	4 (17.4)	2 (8.7)	3 (13.0)	2 (8.7)	5 (21.7)	2 (8.7)	3 (13.0)
Congenital anomaly	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Other	38 (5.2)	91 (12.5)	90 (12.3)	73 (10.0)	112 (15.3)	114 (15.6)	137 (18.8)	75 (10.3)
Absence of reactions[c]								
Absence reported	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	6 (3.4)	16 (9.1)	110 (62.5)	43 (24.4)
No additional terms	5 (1.5)	14 (4.3)	41 (12.5)	16 (4.9)	31 (9.5)	26 (8.0)	171 (52.3)	23 (7.0)

a) cases in 2019 go up to 27 July 2019
b) LE – Lack of efficacy/effect; ME – Medication error; PI – Product Issues; RHA – Reproductive hormone analyses
c) Absence reported – MedDRA terms were reported that indicate that no reaction occurred; No additional terms – Only MedDRA terms from the case definition were reported, no other terms were reported

As noted above, reports may have more than one concern reported. The graph below is called an upset plot. It depicts the counts for all existing combinations. So, for instance, medication errors were reported in 865 reports (horizontal bar) of which 618 were reported without any other concerns of interest (vertical bar) and 170 were reported with product issues.

Importantly, 64 reports mention medication error and lack of effect (36 mention exactly this combination, and the remaining mention a combination of terms, including these). This is 7% of all cases of medication errors and 8% of all cases of lack of effect.

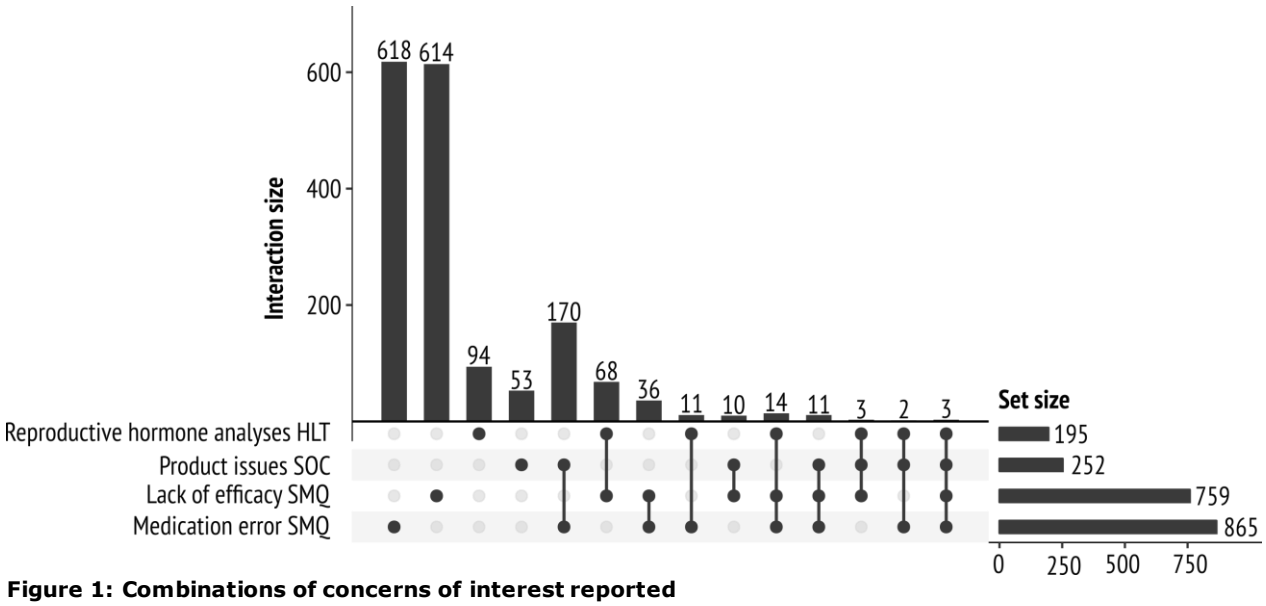

Figure 1: Combinations of concerns of interest reported

The most frequent preferred term for the Lack of effect SMQ was "drug ineffective" with 614 reports (Table 3). The remaining terms are a small proportion of the total, which is expected considering the fact that the SMQ is extremely specific.

On the other hand, the most reported medication error SMQ terms were "inappropriate schedule of product administration" (100), "intercepted medication error" (88) and "wrong technique in product usage process" (88).

Interestingly, in 104 case reports, the blood testosterone increased, with 80% of these being classified as serious.

The complete frequency tables are in the appendix section.

Table 3: Top five MedDRA preferred terms reported by concern of interest, stratified by seriousness. Complete frequency tables are in the appendix.

Concerns of interest	Non-serious report	Serious report	Total
Lack of efficacy/effect SMQ (narrow)			
Drug ineffective	93 (15.1)	521 (84.9)	614
Drug effect decreased	9 (25.7)	26 (74.3)	35
Drug effect incomplete	7 (21.2)	26 (78.8)	33
Drug resistance	3 (17.6)	14 (82.4)	17
Therapeutic response unexpected	8 (50.0)	8 (50.0)	16
Medication error SMQ			
Inappropriate schedule of product administration	18 (18.0)	82 (82.0)	100
Intercepted medication error	84 (95.5)	4 (4.5)	88
Wrong technique in product usage process	53 (60.2)	35 (39.8)	88
Product use in unapproved indication	8 (12.5)	56 (87.5)	64
Product dose omission	17 (27.4)	45 (72.6)	62
Product issues SOC			
Product quality issue	48 (78.7)	13 (21.3)	61
Syringe issue	40 (83.3)	8 (16.7)	48
Device issue	21 (87.5)	3 (12.5)	24

Product complaint	21 (87.5)	3 (12.5)	24
Product leakage	17 (94.4)	1 (5.6)	18
Reproductive hormone analyses HLT			
Blood testosterone increased	20 (19.2)	84 (80.8)	104
Blood testosterone abnormal	15 (37.5)	25 (62.5)	40
Blood testosterone decreased	2 (11.8)	15 (88.2)	17
Blood oestrogen decreased	0 (0.0)	8 (100.0)	8
Blood oestrogen increased	0 (0.0)	8 (100.0)	8

Most reports of the concerns of interest were made in the United States of America (487) (Table 4). The EEA country with the highest count of reports is Germany (189) followed by France (162) and Netherlands (128).

Table 4: Distribution of reports by origin

Origin	Non-serious report	Serious report	Total
Not EEA			
United States of America	12	475	487
Canada	6	109	115
Japan	0	51	51
All others	3	140	143
EEA			
Germany	148	41	189
France	116	46	162
Netherlands	66	62	128
Italy	77	3	80
Sweden	34	42	76
United Kingdom	25	49	74
Spain	22	49	71
Finland	24	2	26
Belgium	5	13	18
Poland	11	4	15
Austria	9	1	10
Greece	4	6	10
Denmark	6	3	9
Bulgaria	2	4	6
Croatia	5	1	6
Ireland	2	4	6
Portugal	4	2	6
Romania	0	6	6
Norway	0	5	5
Hungary	0	3	3
Cyprus	2	0	2
Slovenia	1	1	2
Slovakia	1	0	1

6.2.1. Time trend

The time trend plot (Figure 2) shows that from October 2017, the count of reports in the EEA has increased and overtaking the count of reports from outside the EEA. This increase has been mostly due to non-serious reports. Conversely, outside the EEA the reports have mostly been serious throughout the period 2012 to July 2019.

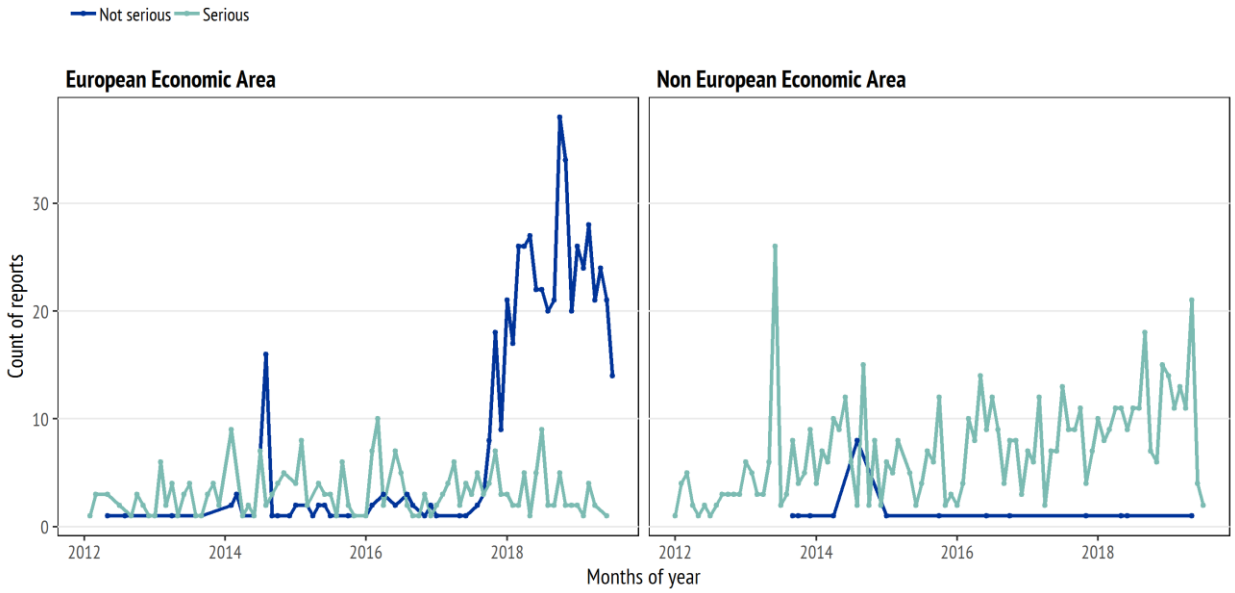

Figure 2: Time trend of reports of the concerns of interest, from 2012 to 2019, stratified by origin of reports

There were 191 reports with MedDRA terms suggesting that no harm occurred or that the medication error was intercepted (Figure 3) (see Appendix for frequency table). A closer look at these cases shows that these have come almost exclusively from the EEA, particularly from October 2017 onwards.

Interestingly, whereas these are intercepted medication errors or did not lead to harm, there are still a few considered serious.

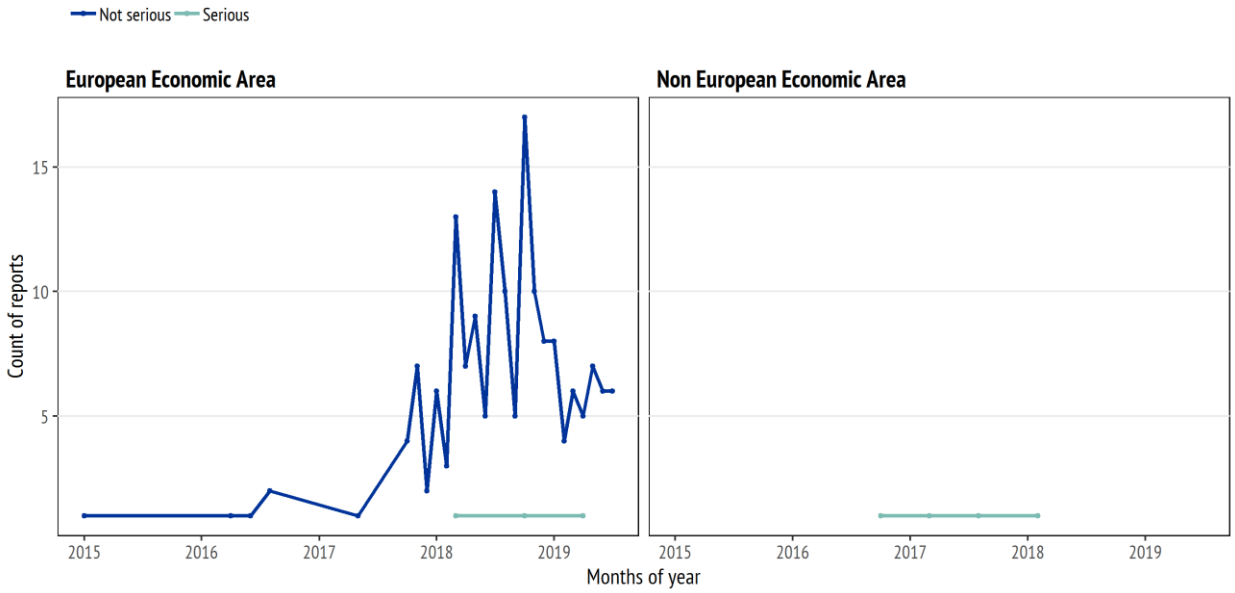

Figure 3: Time trend of reports with the concerns of interest but without harm, from 2012 to 2019, stratified by origin of reports

6.2.2. Time-to-receive

Comparing time-to-receive (i.e. time between reaction start date and receive date) helps understand whether the increases in reporting occur due to increased awareness. It has been noted, in the past that when the reporting of a concern increases following some regulatory action, some of these are historical reports, that happened a while before the receive date but are only reported after the reporter is made aware of the regulatory action.

The distribution of time-to-receive as below does not seem to indicate that historical reports occurred more often during the period of increased reporting (2018 and 2019) (Figure 4).

However, what this method of comparing time-to-report does not capture is the possibility of a diagnostic bias from increased awareness, i.e. that reporters are simply more aware and thus more likely to report.

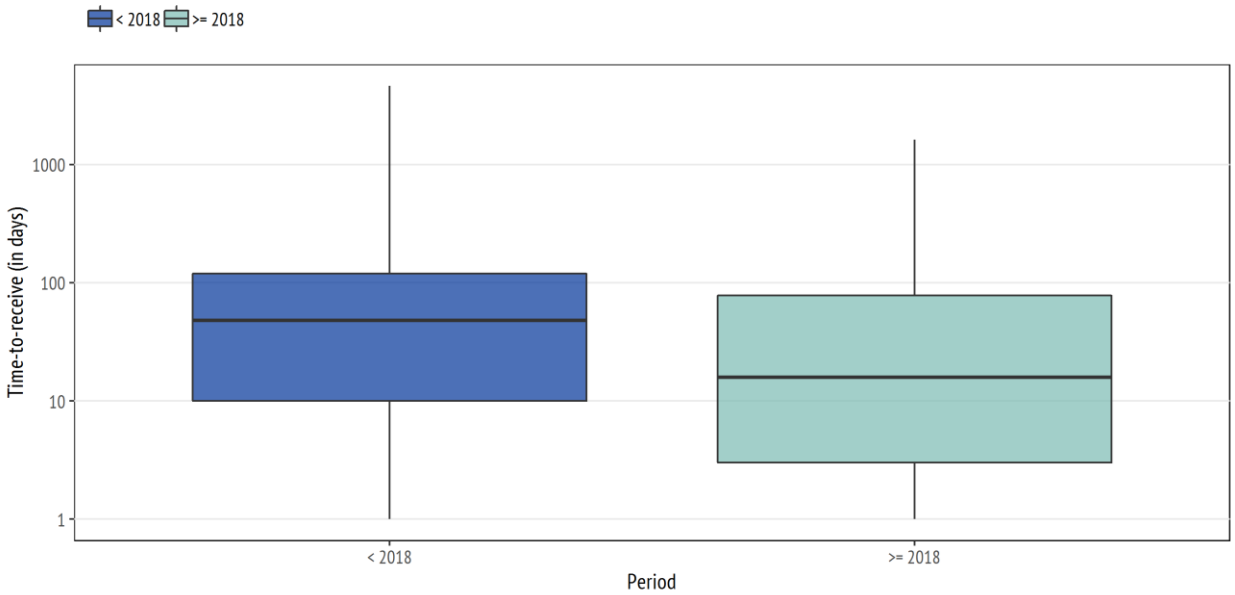

Figure 4: Time-to-receive stratified by <2018 and >=2018.

6.2.3. Disproportionality

Disproportionality was observed for eleven HLTs. In particular, the lower bound of the ROR for the reproductive hormone analyses HLT was very high, at over 30. However, one should bear in mind that this HLT is likely to be specific to only a few medicinal products and the calculation tends to increase the ROR for such products.

Of note, disproportionality was also observed for therapeutic and nontherapeutic responses, which includes the terms of lack of effect, and has the highest count for the calculation of the ROR. In addition, and related to these, Underdoses NEC was also disproportional.

Reaction HLT	ROR(-)	ROR	Count
Disproportionality observed			
Reproductive hormone analyses	30.33904	35.40467	174
Product preparation errors and issues	8.906464	11.61285	56
Occupational exposures	5.52246	9.203019	15
Device physical property and chemical issues	3.047281	3.939213	59
Product prescribing errors and issues	2.90165	3.834466	50
Product selection errors and issues	1.988061	6.205537	3
Product physical issues	1.970763	2.58284	53
Product dispensing errors and issues	1.464373	2.298831	19
Medication errors, product use errors and issues NEC	1.418011	1.583499	325
Therapeutic and nontherapeutic responses	1.045846	1.128385	709
Underdoses NEC	1.011596	1.410225	35
Disproportionality not observed			
Manufacturing materials issues	1.755193	12.75413	1
Product transcribing errors and communication issues	0.943295	6.78064	1
Product quality issues NEC	0.912318	1.124103	89
Product distribution and storage issues	0.802781	5.759886	1
Product administration errors and issues	0.747722	0.849084	243

Pathways and sources of exposure	0.589953	1.574423	4
Device malfunction events NEC	0.53999	0.896377	15
Product storage errors and issues in the product use system	0.488805	0.861353	12
Accidental exposures to product	0.336329	0.607686	11
Non-site specific procedural complications	0.308846	0.434695	33
Product confusion errors and issues	0.29426	1.178539	2
Device issues NEC	0.278947	0.401642	29
Product monitoring errors and issues	0.258689	0.621948	5
Product contamination and sterility issues	0.217541	0.870926	2
Complications associated with device NEC	0.158391	0.316863	8
Overdoses NEC	0.109211	0.15825	28
Product supply and availability issues	0.040335	0.286528	1
Therapeutic drug monitoring analyses	0.03235	0.086217	4
Product packaging issues	0.023842	0.169328	1
Device incompatibility issues	0	0	0

7. Discussion

This review of EudraVigilance suggests that reports of lack of effect, medication errors, product issues and reproductive hormone analyses to leuprorelin have increased considerably in the last 22 months, mostly originating from the EEA.

The majority of these EEA reports are non-serious. In fact, these cases include an increasing number of intercepted medication errors (quasi-incidents) and cases with information that harm did not occur which logically are unlikely to be classified as serious. There were however, a few cases where harm did not occur but the reports were classified as serious.

Sixty-four reports have terms for both medication error and lack of effect combined (some have additional terms within the concerns of interest). This constitutes 7% of all cases of medication errors and 8% of all cases of lack of effect.

The disproportionality analysis also reflects a concern with the reproductive hormone analyses, as well as the likely causes for these, with disproportionalities for the therapeutic and nontherapeutic responses HLT - with includes the term lack of effect - and underdosing NEC HLT.

It is unclear why the counts for these concerns peaked in 2018. It could be a genuine concern with medication error and lack of effect or it could have been due to increased awareness following the 2014 medication error signal and regulatory actions taken, namely the DHPCs, in 2014 and 2017.

In fact, in figure 2, two peaks can be visually identified, one short in 2014 which occurred while the signal was being discussed at PRAC, and the other at the end of 2017. These reports do not seem to be historical reports, but could be still due to increased awareness of the reporters, who will then be more likely to report.

8. Appendix I – list of terms that report absence of harm

MedDRA Preferred term:

- Intercepted medication error
- Intercepted product administration error
- Intercepted product dispensing error
- Intercepted product preparation error
- Intercepted product prescribing error
- Intercepted product selection error
- Intercepted product storage error
- No adverse event

9. Appendix II - Frequency tables of reported terms

9.1. Lack of effect

Lack of efficacy/effect SMQ (narrow)	Non-serious case	Serious case report	Total
Drug ineffective	93 (15.1)	521 (84.9)	614
Drug effect decreased	9 (25.7)	26 (74.3)	35
Drug effect incomplete	7 (21.2)	26 (78.8)	33
Drug resistance	3 (17.6)	14 (82.4)	17
Therapeutic response unexpected	8 (50.0)	8 (50.0)	16
Treatment failure	3 (18.8)	13 (81.2)	16
Therapy non-responder	3 (20.0)	12 (80.0)	15
Therapeutic response decreased	0 (0.0)	9 (100.0)	9
Therapeutic response shortened	1 (16.7)	5 (83.3)	6
Drug effect delayed	0 (0.0)	3 (100.0)	3
Device failure	2 (100.0)	0 (0.0)	2
Therapy partial responder	0 (0.0)	2 (100.0)	2
Device defective	1 (100.0)	0 (0.0)	1
Drug ineffective for unapproved indication	0 (0.0)	1 (100.0)	1
Drug level decreased	0 (0.0)	1 (100.0)	1
Multiple-drug resistance	0 (0.0)	1 (100.0)	1
Paradoxical drug reaction	0 (0.0)	1 (100.0)	1
Therapeutic product ineffective	0 (0.0)	1 (100.0)	1
Therapeutic product ineffective for unapproved indication	1 (100.0)	0 (0.0)	1
Therapeutic response delayed	1 (100.0)	0 (0.0)	1

9.2. Medication error SMQ

Medication error SMQ	Non-serious case	Serious case report	Total
Inappropriate schedule of product administration	18 (18.0)	82 (82.0)	100
Intercepted medication error	84 (95.5)	4 (4.5)	88
Wrong technique in product usage process	53 (60.2)	35 (39.8)	88
Product use in unapproved indication	8 (12.5)	56 (87.5)	64
Product dose omission	17 (27.4)	45 (72.6)	62
Medication error	31 (58.5)	22 (41.5)	53
Syringe issue	40 (83.3)	8 (16.7)	48
Underdose	30 (62.5)	18 (37.5)	48
Incorrect route of product administration	12 (26.1)	34 (73.9)	46
Product administration error	23 (53.5)	20 (46.5)	43
Intercepted product prescribing error	38 (97.4)	1 (2.6)	39
Incorrect dose administered	17 (47.2)	19 (52.8)	36
Intercepted product preparation error	32 (97.0)	1 (3.0)	33
Product use issue	11 (33.3)	22 (66.7)	33
Overdose	9 (31.0)	20 (69.0)	29

Treatment noncompliance	4 (23.5)	13 (76.5)	17
Occupational exposure to product	12 (80.0)	3 (20.0)	15
Product prescribing error	6 (40.0)	9 (60.0)	15
Product preparation issue	7 (58.3)	5 (41.7)	12
Product storage error	4 (33.3)	8 (66.7)	12
Accidental exposure to product	10 (90.9)	1 (9.1)	11
Product preparation error	7 (63.6)	4 (36.4)	11
Needle issue	10 (100.0)	0 (0.0)	10
Product dispensing error	6 (60.0)	4 (40.0)	10
Wrong technique in device usage process	10 (100.0)	0 (0.0)	10
Accidental overdose	1 (11.1)	8 (88.9)	9
Product reconstitution quality issue	3 (33.3)	6 (66.7)	9
Device malfunction	2 (25.0)	6 (75.0)	8
Incorrect product administration duration	0 (0.0)	7 (100.0)	7
Circumstance or information capable of leading to medication error	3 (50.0)	3 (50.0)	6
Extra dose administered	2 (33.3)	4 (66.7)	6
Expired product administered	3 (60.0)	2 (40.0)	5
Injury associated with device	3 (60.0)	2 (40.0)	5
Intercepted product dispensing error	5 (100.0)	0 (0.0)	5
Product administered to patient of inappropriate age	0 (0.0)	5 (100.0)	5
Wrong product administered	2 (40.0)	3 (60.0)	5
Exposure via skin contact	4 (100.0)	0 (0.0)	4
Implantation complication	0 (0.0)	4 (100.0)	4
Intercepted product storage error	4 (100.0)	0 (0.0)	4
Labelled drug-disease interaction medication error	0 (0.0)	4 (100.0)	4
Product administered at inappropriate site	2 (50.0)	2 (50.0)	4
Device dispensing error	3 (100.0)	0 (0.0)	3
Device use error	3 (100.0)	0 (0.0)	3
Intercepted product administration error	2 (66.7)	1 (33.3)	3
Poor quality product administered	0 (0.0)	3 (100.0)	3
Prescribed overdose	1 (33.3)	2 (66.7)	3
Prescribed underdose	0 (0.0)	3 (100.0)	3
Product use complaint	3 (100.0)	0 (0.0)	3
Wrong patient received product	0 (0.0)	3 (100.0)	3
Device difficult to use	2 (100.0)	0 (0.0)	2
Incorrect dose administered by device	2 (100.0)	0 (0.0)	2
Intercepted product selection error	2 (100.0)	0 (0.0)	2
Product name confusion	2 (100.0)	0 (0.0)	2
Product prescribing issue	2 (100.0)	0 (0.0)	2
Complication of device insertion	0 (0.0)	1 (100.0)	1
Contraindicated product administered	0 (0.0)	1 (100.0)	1
Device adhesion issue	1 (100.0)	0 (0.0)	1
Incorrect drug administration rate	0 (0.0)	1 (100.0)	1
Incorrect product dosage form administered	0 (0.0)	1 (100.0)	1
Lack of administration site rotation	1 (100.0)	0 (0.0)	1
Product adhesion issue	0 (0.0)	1 (100.0)	1
Product communication issue	1 (100.0)	0 (0.0)	1
Product dispensing issue	1 (100.0)	0 (0.0)	1

Product monitoring error	1 (100.0)	0 (0.0)	1
Product selection error	1 (100.0)	0 (0.0)	1

9.3. Product issues SOC

Product issues SOC	Non-serious case	Serious case report	Total
Product quality issue	48 (78.7)	13 (21.3)	61
Syringe issue	40 (83.3)	8 (16.7)	48
Device issue	21 (87.5)	3 (12.5)	24
Product complaint	21 (87.5)	3 (12.5)	24
Product leakage	17 (94.4)	1 (5.6)	18
Device occlusion	1 (7.1)	13 (92.9)	14
Product physical consistency issue	14 (100.0)	0 (0.0)	14
Needle issue	10 (100.0)	0 (0.0)	10
Product reconstitution quality issue	3 (33.3)	6 (66.7)	9
Device malfunction	2 (25.0)	6 (75.0)	8
Product physical issue	4 (66.7)	2 (33.3)	6
Product solubility abnormal	4 (80.0)	1 (20.0)	5
Device leakage	1 (33.3)	2 (66.7)	3
Product substitution issue	2 (66.7)	1 (33.3)	3
Device dislocation	0 (0.0)	2 (100.0)	2
Device failure	2 (100.0)	0 (0.0)	2
Product supply issue	0 (0.0)	2 (100.0)	2
Stent malfunction	0 (0.0)	2 (100.0)	2
Device adhesion issue	1 (100.0)	0 (0.0)	1
Device breakage	1 (100.0)	0 (0.0)	1
Device defective	1 (100.0)	0 (0.0)	1
Device expulsion	0 (0.0)	1 (100.0)	1
Device extrusion	0 (0.0)	1 (100.0)	1
Liquid product physical issue	1 (100.0)	0 (0.0)	1
Manufacturing materials issue	1 (100.0)	0 (0.0)	1
Patient-device incompatibility	0 (0.0)	1 (100.0)	1
Product adhesion issue	0 (0.0)	1 (100.0)	1
Product availability issue	1 (100.0)	0 (0.0)	1
Product container seal issue	1 (100.0)	0 (0.0)	1
Product contamination	0 (0.0)	1 (100.0)	1
Product contamination chemical	0 (0.0)	1 (100.0)	1
Product distribution issue	0 (0.0)	1 (100.0)	1
Product formulation issue	1 (100.0)	0 (0.0)	1
Product measured potency issue	1 (100.0)	0 (0.0)	1
Product odour abnormal	0 (0.0)	1 (100.0)	1
Product size issue	0 (0.0)	1 (100.0)	1
Product taste abnormal	0 (0.0)	1 (100.0)	1
Thrombosis in device	0 (0.0)	1 (100.0)	1

9.4. Reproductive hormone analyses HLT

Reproductive hormone analyses HLT	Non-serious case	Serious case report	Total
Blood testosterone increased	20 (19.2)	84 (80.8)	104
Blood testosterone abnormal	15 (37.5)	25 (62.5)	40
Blood testosterone decreased	2 (11.8)	15 (88.2)	17
Blood oestrogen decreased	0 (0.0)	8 (100.0)	8
Blood oestrogen increased	0 (0.0)	8 (100.0)	8
Oestradiol increased	0 (0.0)	7 (100.0)	7
Blood testosterone normal	1 (20.0)	4 (80.0)	5
Progesterone decreased	0 (0.0)	3 (100.0)	3
Oestradiol decreased	0 (0.0)	2 (100.0)	2
Progesterone increased	0 (0.0)	2 (100.0)	2
Blood oestrogen abnormal	0 (0.0)	1 (100.0)	1
Blood testosterone free increased	0 (0.0)	1 (100.0)	1
Human chorionic gonadotropin decreased	0 (0.0)	1 (100.0)	1
Human chorionic gonadotropin increased	0 (0.0)	1 (100.0)	1
Pregnancy test positive	0 (0.0)	1 (100.0)	1

9.5. Reports of absence of harm (based on reported MedDRA term)

Preferred Term	Totals
Intercepted medication error	88
Intercepted product administration error	3
Intercepted product dispensing error	4
Intercepted product preparation error	33
Intercepted product prescribing error	33
Intercepted product selection error	2
Intercepted product storage error	4
No adverse event	24

10. Appendix III – Frequency tables by EEA country

10.1. Austria

	Non serious report (n=23)	Serious report (n=40)	Overall (n=63)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	1 (4.3%)	1 (2.5%)	2 (3.2%)
45 to 64	1 (4.3%)	1 (2.5%)	2 (3.2%)
65 to 74	2 (8.7%)	5 (12.5%)	7 (11.1%)
75 and older	2 (8.7%)	14 (35.0%)	16 (25.4%)
Missing	17 (73.9%)	19 (47.5%)	36 (57.1%)
Gender			
Female	3 (13.0%)	2 (5.0%)	5 (7.9%)
Male	20 (87.0%)	38 (95.0%)	58 (92.1%)
Lack of effect SMQ			
No	19 (82.6%)	39 (97.5%)	58 (92.1%)
Yes	4 (17.4%)	1 (2.5%)	5 (7.9%)
Product issue SOC			
No	21 (91.3%)	40 (100%)	61 (96.8%)
Yes	2 (8.7%)	0 (0%)	2 (3.2%)
Medication error SMQ			
No	17 (73.9%)	40 (100%)	57 (90.5%)
Yes	6 (26.1%)	0 (0%)	6 (9.5%)
Reproductive hormone analyses HLT			
No	22 (95.7%)	40 (100%)	62 (98.4%)
Yes	1 (4.3%)	0 (0%)	1 (1.6%)
Absence of harm reported			
No	21 (91.3%)	40 (100%)	61 (96.8%)
Yes	2 (8.7%)	0 (0%)	2 (3.2%)
No additional terms related to harm			
No	18 (78.3%)	40 (100%)	58 (92.1%)
Yes	5 (21.7%)	0 (0%)	5 (7.9%)

10.2. Belgium

	Non serious report (n=11)	Serious report (n=168)	Overall (n=179)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)	0 (0%)
45 to 64	0 (0%)	3 (1.8%)	3 (1.7%)
65 to 74	1 (9.1%)	7 (4.2%)	8 (4.5%)
75 and older	4 (36.4%)	4 (2.4%)	8 (4.5%)
Missing	6 (54.5%)	154 (91.7%)	160 (89.4%)
Gender			
Female	1 (9.1%)	0 (0%)	1 (0.6%)
Male	9 (81.8%)	153 (91.1%)	162 (90.5%)
Missing	1 (9.1%)	15 (8.9%)	16 (8.9%)
Lack of effect SMQ			
No	11 (100%)	161 (95.8%)	172 (96.1%)
Yes	0 (0%)	7 (4.2%)	7 (3.9%)
Product issue SOC			
No	8 (72.7%)	168 (100%)	176 (98.3%)
Yes	3 (27.3%)	0 (0%)	3 (1.7%)
Medication error SMQ			
No	6 (54.5%)	164 (97.6%)	170 (95.0%)
Yes	5 (45.5%)	4 (2.4%)	9 (5.0%)
Reproductive hormone analyses HLT			
No	11 (100%)	166 (98.8%)	177 (98.9%)
Yes	0 (0%)	2 (1.2%)	2 (1.1%)
Absence of harm reported			
No	10 (90.9%)	168 (100%)	178 (99.4%)
Yes	1 (9.1%)	0 (0%)	1 (0.6%)
No additional terms related to harm			
No	6 (54.5%)	166 (98.8%)	172 (96.1%)
Yes	5 (45.5%)	2 (1.2%)	7 (3.9%)

10.3. Bulgaria

	Non serious report (n=4)	Serious report (n=26)	Overall (n=30)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)	0 (0%)
45 to 64	2 (50.0%)	2 (7.7%)	4 (13.3%)
65 to 74	1 (25.0%)	8 (30.8%)	9 (30.0%)
75 and older	0 (0%)	3 (11.5%)	3 (10.0%)
Missing	1 (25.0%)	13 (50.0%)	14 (46.7%)
Gender			
Female	0 (0%)	0 (0%)	0 (0%)
Male	4 (100%)	25 (96.2%)	29 (96.7%)
Missing	0 (0%)	1 (3.8%)	1 (3.3%)
Lack of effect SMQ			
No	4 (100%)	24 (92.3%)	28 (93.3%)
Yes	0 (0%)	2 (7.7%)	2 (6.7%)
Product issue SOC			
No	3 (75.0%)	26 (100%)	29 (96.7%)
Yes	1 (25.0%)	0 (0%)	1 (3.3%)
Medication error SMQ			
No	2 (50.0%)	23 (88.5%)	25 (83.3%)
Yes	2 (50.0%)	3 (11.5%)	5 (16.7%)
Reproductive hormone analyses HLT			
No	4 (100%)	25 (96.2%)	29 (96.7%)
Yes	0 (0%)	1 (3.8%)	1 (3.3%)
Absence of harm reported			
No	3 (75.0%)	26 (100%)	29 (96.7%)
Yes	1 (25.0%)	0 (0%)	1 (3.3%)
No additional terms related to harm			
No	2 (50.0%)	26 (100%)	28 (93.3%)
Yes	2 (50.0%)	0 (0%)	2 (6.7%)

10.4. Croatia

	Non serious report (n=7)	Serious report (n=2)	Overall (n=9)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)	0 (0%)
45 to 64	1 (14.3%)	0 (0%)	1 (11.1%)
65 to 74	1 (14.3%)	1 (50.0%)	2 (22.2%)
75 and older	0 (0%)	1 (50.0%)	1 (11.1%)
Missing	5 (71.4%)	0 (0%)	5 (55.6%)
Gender			
Female	0 (0%)	0 (0%)	0 (0%)
Male	6 (85.7%)	2 (100%)	8 (88.9%)
Missing	1 (14.3%)	0 (0%)	1 (11.1%)
Lack of effect SMQ			
No	6 (85.7%)	1 (50.0%)	7 (77.8%)
Yes	1 (14.3%)	1 (50.0%)	2 (22.2%)
Product issue SOC			
No	6 (85.7%)	2 (100%)	8 (88.9%)
Yes	1 (14.3%)	0 (0%)	1 (11.1%)
Medication error SMQ			
No	3 (42.9%)	2 (100%)	5 (55.6%)
Yes	4 (57.1%)	0 (0%)	4 (44.4%)
Reproductive hormone analyses HLT			
No	7 (100%)	2 (100%)	9 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Absence of harm reported			
No	5 (71.4%)	2 (100%)	7 (77.8%)
Yes	2 (28.6%)	0 (0%)	2 (22.2%)
No additional terms related to harm			
No	3 (42.9%)	2 (100%)	5 (55.6%)
Yes	4 (57.1%)	0 (0%)	4 (44.4%)

10.5. Cyprus

	Non serious report (n=10)	Overall (n=10)
Age group		
0 to 25	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)
45 to 64	0 (0%)	0 (0%)
65 to 74	4 (40.0%)	4 (40.0%)
75 and older	4 (40.0%)	4 (40.0%)
Missing	2 (20.0%)	2 (20.0%)
Gender		
Female	0 (0%)	0 (0%)
Male	10 (100%)	10 (100%)
Lack of effect SMQ		
No	8 (80.0%)	8 (80.0%)
Yes	2 (20.0%)	2 (20.0%)
Product issue SOC		
No	10 (100%)	10 (100%)
Yes	0 (0%)	0 (0%)
Medication error SMQ		
No	10 (100%)	10 (100%)
Yes	0 (0%)	0 (0%)
Reproductive hormone analyses HLT		
No	10 (100%)	10 (100%)
Yes	0 (0%)	0 (0%)
Absence of harm reported		
No	10 (100%)	10 (100%)
Yes	0 (0%)	0 (0%)
No additional terms related to harm		
No	8 (80.0%)	8 (80.0%)
Yes	2 (20.0%)	2 (20.0%)

10.6. Czech Republic

	Serious report (n=8)	Overall (n=8)
Age group		
0 to 25	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)
45 to 64	5 (62.5%)	5 (62.5%)
65 to 74	1 (12.5%)	1 (12.5%)
75 and older	1 (12.5%)	1 (12.5%)
Missing	1 (12.5%)	1 (12.5%)
Gender		
Female	0 (0%)	0 (0%)
Male	8 (100%)	8 (100%)
Lack of effect SMQ		
No	8 (100%)	8 (100%)
Yes	0 (0%)	0 (0%)
Product issue SOC		
No	8 (100%)	8 (100%)
Yes	0 (0%)	0 (0%)
Medication error SMQ		
No	8 (100%)	8 (100%)
Yes	0 (0%)	0 (0%)
Reproductive hormone analyses HLT		
No	8 (100%)	8 (100%)
Yes	0 (0%)	0 (0%)
Absence of harm reported		
No	8 (100%)	8 (100%)
Yes	0 (0%)	0 (0%)
No additional terms related to harm		
No	8 (100%)	8 (100%)
Yes	0 (0%)	0 (0%)

10.7. Denmark

	Non serious report (n=15)	Serious report (n=30)	Overall (n=45)
Age group			
0 to 25	1 (6.7%)	4 (13.3%)	5 (11.1%)
25 to 44	0 (0%)	0 (0%)	0 (0%)
45 to 64	2 (13.3%)	0 (0%)	2 (4.4%)
65 to 74	3 (20.0%)	6 (20.0%)	9 (20.0%)
75 and older	2 (13.3%)	2 (6.7%)	4 (8.9%)
Missing	7 (46.7%)	18 (60.0%)	25 (55.6%)
Gender			
Female	0 (0%)	11 (36.7%)	11 (24.4%)
Male	15 (100%)	19 (63.3%)	34 (75.6%)
Lack of effect SMQ			
No	15 (100%)	27 (90.0%)	42 (93.3%)
Yes	0 (0%)	3 (10.0%)	3 (6.7%)
Product issue SOC			
No	12 (80.0%)	30 (100%)	42 (93.3%)
Yes	3 (20.0%)	0 (0%)	3 (6.7%)
Medication error SMQ			
No	10 (66.7%)	30 (100%)	40 (88.9%)
Yes	5 (33.3%)	0 (0%)	5 (11.1%)
Reproductive hormone analyses HLT			
No	15 (100%)	30 (100%)	45 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Absence of harm reported			
No	14 (93.3%)	30 (100%)	44 (97.8%)
Yes	1 (6.7%)	0 (0%)	1 (2.2%)
No additional terms related to harm			
No	14 (93.3%)	29 (96.7%)	43 (95.6%)
Yes	1 (6.7%)	1 (3.3%)	2 (4.4%)

10.8. Finland

	Non serious report (n=28)	Serious report (n=24)	Overall (n=52)
Age group			
0 to 25	0 (0%)	1 (4.2%)	1 (1.9%)
25 to 44	0 (0%)	0 (0%)	0 (0%)
45 to 64	0 (0%)	2 (8.3%)	2 (3.8%)
65 to 74	6 (21.4%)	6 (25.0%)	12 (23.1%)
75 and older	3 (10.7%)	10 (41.7%)	13 (25.0%)
Missing	19 (67.9%)	5 (20.8%)	24 (46.2%)
Gender			
Female	2 (7.1%)	1 (4.2%)	3 (5.8%)
Male	22 (78.6%)	22 (91.7%)	44 (84.6%)
Missing	4 (14.3%)	1 (4.2%)	5 (9.6%)
Lack of effect SMQ			
No	25 (89.3%)	22 (91.7%)	47 (90.4%)
Yes	3 (10.7%)	2 (8.3%)	5 (9.6%)
Product issue SOC			
No	12 (42.9%)	24 (100%)	36 (69.2%)
Yes	16 (57.1%)	0 (0%)	16 (30.8%)
Medication error SMQ			
No	5 (17.9%)	24 (100%)	29 (55.8%)
Yes	23 (82.1%)	0 (0%)	23 (44.2%)
Reproductive hormone analyses HLT			
No	28 (100%)	22 (91.7%)	50 (96.2%)
Yes	0 (0%)	2 (8.3%)	2 (3.8%)
Absence of harm reported			
No	23 (82.1%)	24 (100%)	47 (90.4%)
Yes	5 (17.9%)	0 (0%)	5 (9.6%)
No additional terms related to harm			
No	12 (42.9%)	23 (95.8%)	35 (67.3%)
Yes	16 (57.1%)	1 (4.2%)	17 (32.7%)

10.9. France

	Non serious report (n=227)	Serious report (n=581)	Overall (n=808)
Age group			
0 to 25	3 (1.3%)	15 (2.6%)	18 (2.2%)
25 to 44	7 (3.1%)	16 (2.8%)	23 (2.8%)
45 to 64	21 (9.3%)	44 (7.6%)	65 (8.0%)
65 to 74	21 (9.3%)	73 (12.6%)	94 (11.6%)
75 and older	28 (12.3%)	73 (12.6%)	101 (12.5%)
Missing	147 (64.8%)	360 (62.0%)	507 (62.7%)
Gender			
Female	61 (26.9%)	115 (19.8%)	176 (21.8%)
Male	164 (72.2%)	458 (78.8%)	622 (77.0%)
Missing	2 (0.9%)	8 (1.4%)	10 (1.2%)
Lack of effect SMQ			
No	204 (89.9%)	554 (95.4%)	758 (93.8%)
Yes	23 (10.1%)	27 (4.6%)	50 (6.2%)
Product issue SOC			
No	183 (80.6%)	575 (99.0%)	758 (93.8%)
Yes	44 (19.4%)	6 (1.0%)	50 (6.2%)
Medication error SMQ			
No	143 (63.0%)	560 (96.4%)	703 (87.0%)
Yes	84 (37.0%)	21 (3.6%)	105 (13.0%)
Reproductive hormone analyses HLT			
No	211 (93.0%)	575 (99.0%)	786 (97.3%)
Yes	16 (7.0%)	6 (1.0%)	22 (2.7%)
Absence of harm reported			
No	214 (94.3%)	579 (99.7%)	793 (98.1%)
Yes	13 (5.7%)	2 (0.3%)	15 (1.9%)
No additional terms related to harm			
No	178 (78.4%)	568 (97.8%)	746 (92.3%)
Yes	49 (21.6%)	13 (2.2%)	62 (7.7%)

10.10. Germany

	Non serious report (n=608)	Serious report (n=653)	Overall (n=1261)
Age group			
0 to 25	26 (4.3%)	17 (2.6%)	43 (3.4%)
25 to 44	22 (3.6%)	37 (5.7%)	59 (4.7%)
45 to 64	57 (9.4%)	76 (11.6%)	133 (10.5%)
65 to 74	130 (21.4%)	157 (24.0%)	287 (22.8%)
75 and older	143 (23.5%)	203 (31.1%)	346 (27.4%)
Missing	230 (37.8%)	163 (25.0%)	393 (31.2%)
Gender			
Female	95 (15.6%)	61 (9.3%)	156 (12.4%)
Male	504 (82.9%)	582 (89.1%)	1086 (86.1%)
Missing	9 (1.5%)	10 (1.5%)	19 (1.5%)
Lack of effect SMQ			
No	589 (96.9%)	629 (96.3%)	1218 (96.6%)
Yes	19 (3.1%)	24 (3.7%)	43 (3.4%)
Product issue SOC			
No	563 (92.6%)	648 (99.2%)	1211 (96.0%)
Yes	45 (7.4%)	5 (0.8%)	50 (4.0%)
Medication error SMQ			
No	481 (79.1%)	639 (97.9%)	1120 (88.8%)
Yes	127 (20.9%)	14 (2.1%)	141 (11.2%)
Reproductive hormone analyses HLT			
No	601 (98.8%)	647 (99.1%)	1248 (99.0%)
Yes	7 (1.2%)	6 (0.9%)	13 (1.0%)
Absence of harm reported			
No	541 (89.0%)	653 (100%)	1194 (94.7%)
Yes	67 (11.0%)	0 (0%)	67 (5.3%)
No additional terms related to harm			
No	576 (94.7%)	643 (98.5%)	1219 (96.7%)
Yes	32 (5.3%)	10 (1.5%)	42 (3.3%)

10.11. Greece

	Non serious report (n=11)	Serious report (n=22)	Overall (n=33)
Age group			
0 to 25	0 (0%)	2 (9.1%)	2 (6.1%)
25 to 44	1 (9.1%)	9 (40.9%)	10 (30.3%)
45 to 64	1 (9.1%)	2 (9.1%)	3 (9.1%)
65 to 74	3 (27.3%)	0 (0%)	3 (9.1%)
75 and older	0 (0%)	2 (9.1%)	2 (6.1%)
Missing	6 (54.5%)	7 (31.8%)	13 (39.4%)
Gender			
Female	2 (18.2%)	14 (63.6%)	16 (48.5%)
Male	8 (72.7%)	7 (31.8%)	15 (45.5%)
Missing	1 (9.1%)	1 (4.5%)	2 (6.1%)
Lack of effect SMQ			
No	11 (100%)	20 (90.9%)	31 (93.9%)
Yes	0 (0%)	2 (9.1%)	2 (6.1%)
Product issue SOC			
No	9 (81.8%)	21 (95.5%)	30 (90.9%)
Yes	2 (18.2%)	1 (4.5%)	3 (9.1%)
Medication error SMQ			
No	8 (72.7%)	19 (86.4%)	27 (81.8%)
Yes	3 (27.3%)	3 (13.6%)	6 (18.2%)
Reproductive hormone analyses HLT			
No	10 (90.9%)	22 (100%)	32 (97.0%)
Yes	1 (9.1%)	0 (0%)	1 (3.0%)
Absence of harm reported			
No	11 (100%)	22 (100%)	33 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
No additional terms related to harm			
No	8 (72.7%)	22 (100%)	30 (90.9%)
Yes	3 (27.3%)	0 (0%)	3 (9.1%)

10.12. Hungary

	Non serious report (n=3)	Serious report (n=57)	Overall (n=60)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	1 (1.8%)	1 (1.7%)
45 to 64	1 (33.3%)	0 (0%)	1 (1.7%)
65 to 74	0 (0%)	1 (1.8%)	1 (1.7%)
75 and older	0 (0%)	1 (1.8%)	1 (1.7%)
Missing	2 (66.7%)	54 (94.7%)	56 (93.3%)
Gender			
Female	0 (0%)	1 (1.8%)	1 (1.7%)
Male	3 (100%)	56 (98.2%)	59 (98.3%)
Lack of effect SMQ			
No	3 (100%)	54 (94.7%)	57 (95.0%)
Yes	0 (0%)	3 (5.3%)	3 (5.0%)
Product issue SOC			
No	3 (100%)	57 (100%)	60 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Medication error SMQ			
No	3 (100%)	57 (100%)	60 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Reproductive hormone analyses HLT			
No	3 (100%)	57 (100%)	60 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Absence of harm reported			
No	3 (100%)	57 (100%)	60 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
No additional terms related to harm			
No	3 (100%)	57 (100%)	60 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)

10.13. Iceland

	Serious report (n=1)	Overall (n=1)
Age group		
0 to 25	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)
45 to 64	0 (0%)	0 (0%)
65 to 74	1 (100%)	1 (100%)
75 and older	0 (0%)	0 (0%)
Gender		
Female	0 (0%)	0 (0%)
Male	1 (100%)	1 (100%)
Lack of effect SMQ		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Product issue SOC		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Medication error SMQ		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Reproductive hormone analyses HLT		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Absence of harm reported		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
No additional terms related to harm		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)

10.14. Ireland

	Non serious report (n=2)	Serious report (n=18)	Overall (n=20)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)	0 (0%)
45 to 64	0 (0%)	1 (5.6%)	1 (5.0%)
65 to 74	0 (0%)	1 (5.6%)	1 (5.0%)
75 and older	0 (0%)	1 (5.6%)	1 (5.0%)
Missing	2 (100%)	15 (83.3%)	17 (85.0%)
Gender			
Female	0 (0%)	0 (0%)	0 (0%)
Male	2 (100%)	18 (100%)	20 (100%)
Lack of effect SMQ			
No	2 (100%)	17 (94.4%)	19 (95.0%)
Yes	0 (0%)	1 (5.6%)	1 (5.0%)
Product issue SOC			
No	0 (0%)	17 (94.4%)	17 (85.0%)
Yes	2 (100%)	1 (5.6%)	3 (15.0%)
Medication error SMQ			
No	0 (0%)	15 (83.3%)	15 (75.0%)
Yes	2 (100%)	3 (16.7%)	5 (25.0%)
Reproductive hormone analyses HLT			
No	2 (100%)	18 (100%)	20 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Absence of harm reported			
No	0 (0%)	18 (100%)	18 (90.0%)
Yes	2 (100%)	0 (0%)	2 (10.0%)
No additional terms related to harm			
No	0 (0%)	18 (100%)	18 (90.0%)
Yes	2 (100%)	0 (0%)	2 (10.0%)

10.15. Italy

	Non serious report (n=205)	Serious report (n=85)	Overall (n=290)
Age group			
0 to 25	2 (1.0%)	1 (1.2%)	3 (1.0%)
25 to 44	13 (6.3%)	23 (27.1%)	36 (12.4%)
45 to 64	16 (7.8%)	13 (15.3%)	29 (10.0%)
65 to 74	21 (10.2%)	2 (2.4%)	23 (7.9%)
75 and older	14 (6.8%)	13 (15.3%)	27 (9.3%)
Missing	139 (67.8%)	33 (38.8%)	172 (59.3%)
Gender			
Female	85 (41.5%)	44 (51.8%)	129 (44.5%)
Male	119 (58.0%)	40 (47.1%)	159 (54.8%)
Missing	1 (0.5%)	1 (1.2%)	2 (0.7%)
Lack of effect SMQ			
No	195 (95.1%)	83 (97.6%)	278 (95.9%)
Yes	10 (4.9%)	2 (2.4%)	12 (4.1%)
Product issue SOC			
No	191 (93.2%)	85 (100%)	276 (95.2%)
Yes	14 (6.8%)	0 (0%)	14 (4.8%)
Medication error SMQ			
No	139 (67.8%)	84 (98.8%)	223 (76.9%)
Yes	66 (32.2%)	1 (1.2%)	67 (23.1%)
Reproductive hormone analyses HLT			
No	203 (99.0%)	84 (98.8%)	287 (99.0%)
Yes	2 (1.0%)	1 (1.2%)	3 (1.0%)
Absence of harm reported			
No	154 (75.1%)	85 (100%)	239 (82.4%)
Yes	51 (24.9%)	0 (0%)	51 (17.6%)
No additional terms related to harm			
No	186 (90.7%)	83 (97.6%)	269 (92.8%)
Yes	19 (9.3%)	2 (2.4%)	21 (7.2%)

10.16. Lithuania

	Serious report (n=2)	Overall (n=2)
Age group		
0 to 25	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)
45 to 64	1 (50.0%)	1 (50.0%)
65 to 74	0 (0%)	0 (0%)
75 and older	0 (0%)	0 (0%)
Missing	1 (50.0%)	1 (50.0%)
Gender		
Female	0 (0%)	0 (0%)
Male	2 (100%)	2 (100%)
Lack of effect SMQ		
No	2 (100%)	2 (100%)
Yes	0 (0%)	0 (0%)
Product issue SOC		
No	2 (100%)	2 (100%)
Yes	0 (0%)	0 (0%)
Medication error SMQ		
No	2 (100%)	2 (100%)
Yes	0 (0%)	0 (0%)
Reproductive hormone analyses HLT		
No	2 (100%)	2 (100%)
Yes	0 (0%)	0 (0%)
Absence of harm reported		
No	2 (100%)	2 (100%)
Yes	0 (0%)	0 (0%)
No additional terms related to harm		
No	2 (100%)	2 (100%)
Yes	0 (0%)	0 (0%)

10.17. Malta

	Serious report (n=1)	Overall (n=1)
Age group		
0 to 25	1 (100%)	1 (100%)
25 to 44	0 (0%)	0 (0%)
45 to 64	0 (0%)	0 (0%)
65 to 74	0 (0%)	0 (0%)
75 and older	0 (0%)	0 (0%)
Gender		
Female	1 (100%)	1 (100%)
Male	0 (0%)	0 (0%)
Lack of effect SMQ		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Product issue SOC		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Medication error SMQ		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Reproductive hormone analyses HLT		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
Absence of harm reported		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)
No additional terms related to harm		
No	1 (100%)	1 (100%)
Yes	0 (0%)	0 (0%)

10.18. Netherlands

	Non serious report (n=995)	Serious report (n=2377)	Overall (n=3372)
Age group			
0 to 25	8 (0.8%)	4 (0.2%)	12 (0.4%)
25 to 44	46 (4.6%)	7 (0.3%)	53 (1.6%)
45 to 64	34 (3.4%)	12 (0.5%)	46 (1.4%)
65 to 74	22 (2.2%)	10 (0.4%)	32 (0.9%)
75 and older	19 (1.9%)	27 (1.1%)	46 (1.4%)
Missing	866 (87.0%)	2317 (97.5%)	3183 (94.4%)
Gender			
Female	568 (57.1%)	270 (11.4%)	838 (24.9%)
Male	424 (42.6%)	2017 (84.9%)	2441 (72.4%)
Missing	3 (0.3%)	90 (3.8%)	93 (2.8%)
Lack of effect SMQ			
No	959 (96.4%)	2346 (98.7%)	3305 (98.0%)
Yes	36 (3.6%)	31 (1.3%)	67 (2.0%)
Product issue SOC			
No	987 (99.2%)	2373 (99.8%)	3360 (99.6%)
Yes	8 (0.8%)	4 (0.2%)	12 (0.4%)
Medication error SMQ			
No	967 (97.2%)	2349 (98.8%)	3316 (98.3%)
Yes	28 (2.8%)	28 (1.2%)	56 (1.7%)
Reproductive hormone analyses HLT			
No	992 (99.7%)	2377 (100%)	3369 (99.9%)
Yes	3 (0.3%)	0 (0%)	3 (0.1%)
Absence of harm reported			
No	993 (99.8%)	2376 (100.0%)	3369 (99.9%)
Yes	2 (0.2%)	1 (0.0%)	3 (0.1%)
No additional terms related to harm			
No	984 (98.9%)	2374 (99.9%)	3358 (99.6%)
Yes	11 (1.1%)	3 (0.1%)	14 (0.4%)

10.19. Norway

	Non serious report (n=2)	Serious report (n=17)	Overall (n=19)
Age group			
0 to 25	1 (50.0%)	1 (5.9%)	2 (10.5%)
25 to 44	0 (0%)	3 (17.6%)	3 (15.8%)
45 to 64	0 (0%)	4 (23.5%)	4 (21.1%)
65 to 74	0 (0%)	2 (11.8%)	2 (10.5%)
75 and older	0 (0%)	4 (23.5%)	4 (21.1%)
Missing	1 (50.0%)	3 (17.6%)	4 (21.1%)
Gender			
Female	2 (100%)	2 (11.8%)	4 (21.1%)
Male	0 (0%)	15 (88.2%)	15 (78.9%)
Lack of effect SMQ			
No	2 (100%)	12 (70.6%)	14 (73.7%)
Yes	0 (0%)	5 (29.4%)	5 (26.3%)
Product issue SOC			
No	2 (100%)	17 (100%)	19 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Medication error SMQ			
No	2 (100%)	17 (100%)	19 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Reproductive hormone analyses HLT			
No	2 (100%)	16 (94.1%)	18 (94.7%)
Yes	0 (0%)	1 (5.9%)	1 (5.3%)
Absence of harm reported			
No	2 (100%)	17 (100%)	19 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
No additional terms related to harm			
No	2 (100%)	12 (70.6%)	14 (73.7%)
Yes	0 (0%)	5 (29.4%)	5 (26.3%)

10.20. Poland

	Non serious report (n=26)	Serious report (n=51)	Overall (n=77)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	3 (5.9%)	3 (3.9%)
45 to 64	4 (15.4%)	12 (23.5%)	16 (20.8%)
65 to 74	8 (30.8%)	15 (29.4%)	23 (29.9%)
75 and older	7 (26.9%)	10 (19.6%)	17 (22.1%)
Missing	7 (26.9%)	11 (21.6%)	18 (23.4%)
Gender			
Female	1 (3.8%)	2 (3.9%)	3 (3.9%)
Male	25 (96.2%)	47 (92.2%)	72 (93.5%)
Missing	0 (0%)	2 (3.9%)	2 (2.6%)
Lack of effect SMQ			
No	25 (96.2%)	49 (96.1%)	74 (96.1%)
Yes	1 (3.8%)	2 (3.9%)	3 (3.9%)
Product issue SOC			
No	20 (76.9%)	51 (100%)	71 (92.2%)
Yes	6 (23.1%)	0 (0%)	6 (7.8%)
Medication error SMQ			
No	16 (61.5%)	49 (96.1%)	65 (84.4%)
Yes	10 (38.5%)	2 (3.9%)	12 (15.6%)
Reproductive hormone analyses HLT			
No	26 (100%)	51 (100%)	77 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Absence of harm reported			
No	20 (76.9%)	51 (100%)	71 (92.2%)
Yes	6 (23.1%)	0 (0%)	6 (7.8%)
No additional terms related to harm			
No	19 (73.1%)	51 (100%)	70 (90.9%)
Yes	7 (26.9%)	0 (0%)	7 (9.1%)

10.21. Portugal

	Non serious report (n=9)	Serious report (n=17)	Overall (n=26)
Age group			
0 to 25	1 (11.1%)	1 (5.9%)	2 (7.7%)
25 to 44	0 (0%)	1 (5.9%)	1 (3.8%)
45 to 64	0 (0%)	1 (5.9%)	1 (3.8%)
65 to 74	0 (0%)	2 (11.8%)	2 (7.7%)
75 and older	0 (0%)	4 (23.5%)	4 (15.4%)
Missing	8 (88.9%)	8 (47.1%)	16 (61.5%)
Gender			
Female	1 (11.1%)	3 (17.6%)	4 (15.4%)
Male	8 (88.9%)	14 (82.4%)	22 (84.6%)
Lack of effect SMQ			
No	9 (100%)	16 (94.1%)	25 (96.2%)
Yes	0 (0%)	1 (5.9%)	1 (3.8%)
Product issue SOC			
No	7 (77.8%)	17 (100%)	24 (92.3%)
Yes	2 (22.2%)	0 (0%)	2 (7.7%)
Medication error SMQ			
No	5 (55.6%)	16 (94.1%)	21 (80.8%)
Yes	4 (44.4%)	1 (5.9%)	5 (19.2%)
Reproductive hormone analyses HLT			
No	9 (100%)	17 (100%)	26 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Absence of harm reported			
No	7 (77.8%)	17 (100%)	24 (92.3%)
Yes	2 (22.2%)	0 (0%)	2 (7.7%)
No additional terms related to harm			
No	7 (77.8%)	16 (94.1%)	23 (88.5%)
Yes	2 (22.2%)	1 (5.9%)	3 (11.5%)

10.22. Romania

	Serious report (n=28)	Overall (n=28)
Age group		
0 to 25	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)
45 to 64	2 (7.1%)	2 (7.1%)
65 to 74	3 (10.7%)	3 (10.7%)
75 and older	3 (10.7%)	3 (10.7%)
Missing	20 (71.4%)	20 (71.4%)
Gender		
Female	0 (0%)	0 (0%)
Male	27 (96.4%)	27 (96.4%)
Missing	1 (3.6%)	1 (3.6%)
Lack of effect SMQ		
No	24 (85.7%)	24 (85.7%)
Yes	4 (14.3%)	4 (14.3%)
Product issue SOC		
No	28 (100%)	28 (100%)
Yes	0 (0%)	0 (0%)
Medication error SMQ		
No	27 (96.4%)	27 (96.4%)
Yes	1 (3.6%)	1 (3.6%)
Reproductive hormone analyses HLT		
No	27 (96.4%)	27 (96.4%)
Yes	1 (3.6%)	1 (3.6%)
Absence of harm reported		
No	28 (100%)	28 (100%)
Yes	0 (0%)	0 (0%)
No additional terms related to harm		
No	28 (100%)	28 (100%)
Yes	0 (0%)	0 (0%)

10.23. Slovakia

	Non serious report (n=1)	Serious report (n=4)	Overall (n=5)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	1 (25.0%)	1 (20.0%)
45 to 64	0 (0%)	1 (25.0%)	1 (20.0%)
65 to 74	0 (0%)	2 (50.0%)	2 (40.0%)
75 and older	0 (0%)	0 (0%)	0 (0%)
Missing	1 (100%)	0 (0%)	1 (20.0%)
Gender			
Female	0 (0%)	1 (25.0%)	1 (20.0%)
Male	1 (100%)	3 (75.0%)	4 (80.0%)
Lack of effect SMQ			
No	1 (100%)	4 (100%)	5 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Product issue SOC			
No	0 (0%)	4 (100%)	4 (80.0%)
Yes	1 (100%)	0 (0%)	1 (20.0%)
Medication error SMQ			
No	0 (0%)	4 (100%)	4 (80.0%)
Yes	1 (100%)	0 (0%)	1 (20.0%)
Reproductive hormone analyses HLT			
No	1 (100%)	4 (100%)	5 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Absence of harm reported			
No	0 (0%)	4 (100%)	4 (80.0%)
Yes	1 (100%)	0 (0%)	1 (20.0%)
No additional terms related to harm			
No	0 (0%)	4 (100%)	4 (80.0%)
Yes	1 (100%)	0 (0%)	1 (20.0%)

10.24. Slovenia

	Non serious report (n=1)	Serious report (n=18)	Overall (n=19)
Age group			
0 to 25	0 (0%)	0 (0%)	0 (0%)
25 to 44	0 (0%)	0 (0%)	0 (0%)
45 to 64	0 (0%)	0 (0%)	0 (0%)
65 to 74	0 (0%)	1 (5.6%)	1 (5.3%)
75 and older	0 (0%)	3 (16.7%)	3 (15.8%)
Missing	1 (100%)	14 (77.8%)	15 (78.9%)
Gender			
Female	0 (0%)	0 (0%)	0 (0%)
Male	1 (100%)	18 (100%)	19 (100%)
Lack of effect SMQ			
No	0 (0%)	18 (100%)	18 (94.7%)
Yes	1 (100%)	0 (0%)	1 (5.3%)
Product issue SOC			
No	1 (100%)	18 (100%)	19 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Medication error SMQ			
No	1 (100%)	18 (100%)	19 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Reproductive hormone analyses HLT			
No	1 (100%)	17 (94.4%)	18 (94.7%)
Yes	0 (0%)	1 (5.6%)	1 (5.3%)
Absence of harm reported			
No	1 (100%)	18 (100%)	19 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
No additional terms related to harm			
No	1 (100%)	17 (94.4%)	18 (94.7%)
Yes	0 (0%)	1 (5.6%)	1 (5.3%)

10.25. Spain

	Non serious report (n=29)	Serious report (n=163)	Overall (n=192)
Age group			
0 to 25	0 (0%)	1 (0.6%)	1 (0.5%)
25 to 44	0 (0%)	9 (5.5%)	9 (4.7%)
45 to 64	1 (3.4%)	20 (12.3%)	21 (10.9%)
65 to 74	2 (6.9%)	39 (23.9%)	41 (21.4%)
75 and older	4 (13.8%)	54 (33.1%)	58 (30.2%)
Missing	22 (75.9%)	40 (24.5%)	62 (32.3%)
Gender			
Female	0 (0%)	10 (6.1%)	10 (5.2%)
Male	28 (96.6%)	151 (92.6%)	179 (93.2%)
Missing	1 (3.4%)	2 (1.2%)	3 (1.6%)
Lack of effect SMQ			
No	27 (93.1%)	124 (76.1%)	151 (78.6%)
Yes	2 (6.9%)	39 (23.9%)	41 (21.4%)
Product issue SOC			
No	20 (69.0%)	163 (100%)	183 (95.3%)
Yes	9 (31.0%)	0 (0%)	9 (4.7%)
Medication error SMQ			
No	8 (27.6%)	154 (94.5%)	162 (84.4%)
Yes	21 (72.4%)	9 (5.5%)	30 (15.6%)
Reproductive hormone analyses HLT			
No	26 (89.7%)	148 (90.8%)	174 (90.6%)
Yes	3 (10.3%)	15 (9.2%)	18 (9.4%)
Absence of harm reported			
No	16 (55.2%)	163 (100%)	179 (93.2%)
Yes	13 (44.8%)	0 (0%)	13 (6.8%)
No additional terms related to harm			
No	9 (31.0%)	128 (78.5%)	137 (71.4%)
Yes	20 (69.0%)	35 (21.5%)	55 (28.6%)

10.26. Sweden

	Non serious report (n=48)	Serious report (n=102)	Overall (n=150)
Age group			
0 to 25	0 (0%)	4 (3.9%)	4 (2.7%)
25 to 44	12 (25.0%)	5 (4.9%)	17 (11.3%)
45 to 64	5 (10.4%)	8 (7.8%)	13 (8.7%)
65 to 74	1 (2.1%)	32 (31.4%)	33 (22.0%)
75 and older	5 (10.4%)	25 (24.5%)	30 (20.0%)
Missing	25 (52.1%)	28 (27.5%)	53 (35.3%)
Gender			
Female	6 (12.5%)	10 (9.8%)	16 (10.7%)
Male	39 (81.2%)	92 (90.2%)	131 (87.3%)
Missing	3 (6.2%)	0 (0%)	3 (2.0%)
Lack of effect SMQ			
No	35 (72.9%)	64 (62.7%)	99 (66.0%)
Yes	13 (27.1%)	38 (37.3%)	51 (34.0%)
Product issue SOC			
No	33 (68.8%)	97 (95.1%)	130 (86.7%)
Yes	15 (31.2%)	5 (4.9%)	20 (13.3%)
Medication error SMQ			
No	28 (58.3%)	94 (92.2%)	122 (81.3%)
Yes	20 (41.7%)	8 (7.8%)	28 (18.7%)
Reproductive hormone analyses HLT			
No	48 (100%)	101 (99.0%)	149 (99.3%)
Yes	0 (0%)	1 (1.0%)	1 (0.7%)
Absence of harm reported			
No	46 (95.8%)	102 (100%)	148 (98.7%)
Yes	2 (4.2%)	0 (0%)	2 (1.3%)
No additional terms related to harm			
No	23 (47.9%)	67 (65.7%)	90 (60.0%)
Yes	25 (52.1%)	35 (34.3%)	60 (40.0%)

10.27. United Kingdom

	Non serious report (n=68)	Serious report (n=342)	Overall (n=410)
Age group			
0 to 25	2 (2.9%)	10 (2.9%)	12 (2.9%)
25 to 44	6 (8.8%)	60 (17.5%)	66 (16.1%)
45 to 64	8 (11.8%)	65 (19.0%)	73 (17.8%)
65 to 74	7 (10.3%)	53 (15.5%)	60 (14.6%)
75 and older	8 (11.8%)	76 (22.2%)	84 (20.5%)
Missing	37 (54.4%)	78 (22.8%)	115 (28.0%)
Gender			
Female	23 (33.8%)	114 (33.3%)	137 (33.4%)
Male	43 (63.2%)	219 (64.0%)	262 (63.9%)
Missing	2 (2.9%)	9 (2.6%)	11 (2.7%)
Lack of effect SMQ			
No	62 (91.2%)	321 (93.9%)	383 (93.4%)
Yes	6 (8.8%)	21 (6.1%)	27 (6.6%)
Product issue SOC			
No	65 (95.6%)	340 (99.4%)	405 (98.8%)
Yes	3 (4.4%)	2 (0.6%)	5 (1.2%)
Medication error SMQ			
No	49 (72.1%)	316 (92.4%)	365 (89.0%)
Yes	19 (27.9%)	26 (7.6%)	45 (11.0%)
Reproductive hormone analyses HLT			
No	67 (98.5%)	335 (98.0%)	402 (98.0%)
Yes	1 (1.5%)	7 (2.0%)	8 (2.0%)
Absence of harm reported			
No	68 (100%)	342 (100%)	410 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
No additional terms related to harm			
No	66 (97.1%)	335 (98.0%)	401 (97.8%)
Yes	2 (2.9%)	7 (2.0%)	9 (2.2%)