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## Retinoid-containing medicinal products Art.31 referral

Analysis of case reports in EudraVigilance to inform decision making in the context of a referral procedure

|                           |                                                                                                                                                                                                          |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Substance(s) (INN)</b> | Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tretinoin, Tazarotene                                                                                                                      |
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| <b>Date of report</b>     | 22/09/2016                                                                                                                                                                                               |



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## 1. List of abbreviations

EEA: European Economic Area

EMA: European Medicines Agency

EV: EudraVigilance

EVCTM: EudraVigilance Clinical Trial module

EVPM: EudraVigilance Post-Authorisation module

INN: International Non-proprietary Nomenclature

MAH: Marketing Authorisation Holder

MedDRA: Medical Dictionary for Regulatory Activities

PRAC: Pharmacovigilance Risk Assessment Committee

PRR: Proportional reporting ratio

PT: MedDRA Preferred Term

SMQ: Standardised MedDRA Query

SOC: MedDRA System Organ Class

SmPC: Summary of Product Characteristics

## 2. Responsible parties

| Responsible parties    | Name                              |
|------------------------|-----------------------------------|
| Lead investigator      | Luis Pinheiro                     |
| Product identification | Loris Piccolo                     |
| Data quality           | Tom Paternoster-Howe              |
| Data analysis          | Luis Pinheiro and Irina Caplanusi |
| Product team Member    | Ana Zanoletty Perez               |
| Peer-review            | Georgy Genov                      |
| Sign-off               | Peter Arlett                      |

## 3. Milestones

| Steps                                         | Planned date | Actual date |
|-----------------------------------------------|--------------|-------------|
| Draft analysis plan sent to Rapporteurs       |              | 20/01/2021  |
| Data quality check (de-duplication, recoding) | 22/07/2016   | 19/07/2016  |
| Exploratory analysis                          | 31/08/2016   | 31/08/2016  |

| Steps                   | Planned date | Actual date |
|-------------------------|--------------|-------------|
| Analysis completed      | 15/09/2016   | 22/09/2016  |
| Study report completed  | 21/09/2016   | 23/09/2016  |
| Study report signed-off | 23/09/2016   | 27/09/2016  |

## 4. Introduction and background

On 8 July 2016 the Medicines and Healthcare Products Regulatory Agency (MHRA) identified the need for detailed assessment of the possible risk of neuropsychiatric disorders associated with the use of retinoid products and referred the matter to the Pharmacovigilance Risk Assessment Committee (PRAC). Warnings about this possible risk are already included in the product information for some of these medicines. The Committee will review the extent and nature of these warnings to ensure that they reflect the available evidence for oral and topical retinoids.

In addition, the PRAC will concomitantly conduct a review of the measures currently in place for pregnancy prevention for retinoid containing medicinal products, including the warnings and recommendations in the product information, to ensure that they are effective and appropriate.

As retinoid-containing medicinal products are marketed by several MAHs, the data that will be provided by the MAHs will be truncated according to each MAH's own reports. Hence, in view of providing a more comprehensive overview of the evidence available the Signal and Incident Management team initiated an analysis of the EudraVigilance data.

## 5. Aims

The aim of the EudraVigilance analysis is to provide a comprehensive overview of the case reports of neuropsychiatric adverse events associated with the use of retinoid-containing medicinal products.

## 6. Methodology

### 6.1. Case definitions

#### 6.1.1. Neuropsychiatric reaction

A case report was considered as a report of a neuropsychiatric reaction if any preferred term from the SOC Psychiatric disorders was reported.

#### 6.1.2. Self-injury-specific mortality

Psychiatric disorders typically only lead to fatal outcome when self-destructive behaviour occurs, i.e. suicide. However, other adverse reactions that lead to a fatal outcome may be reported in the case reports (e.g. toxic epidermal necrolysis), hence a case's seriousness may be coded as fatal but not be related to self-injury. To differentiate cases where the patient died from a different reaction, we report on the self-injury-specific mortality by selecting the reaction outcome field [ICH E2B(R2) B.2.i.8] rather than reporting on the seriousness field [ICH E2B(R2) A.1.5.2.]

Case reports were thus considered as a fatal case of self-injury where the outcome of a reported preferred term from the Depression and suicide/self-injury level 1 SMQ was fatal or the report included the MedDRA term Completed suicide.

## 6.2. Classification of exposure

Each individual retinoid may have more than one reported Scientific Composition (High Level), e.g. *isotretinoin* and *erythromycin, isotretinoin*. To facilitate comparison, we grouped Scientific Compositions (High Level) under the respective INN, hence all combinations containing specific retinoids are reported under the respective retinoid's INN (e.g. *Isotretinoin* contains case reports for *isotretinoin* and *erythromycin, isotretinoin*).

## 6.3. EudraVigilance search strategy

Data quality verification (de-duplication, recoding of medicinal products) was conducted in July 2016 to ensure a reliable data set for the conduct of the analysis and was concluded on 19 July 2016.

EudraVigilance was queried for all case of neuropsychiatric disorders reported in association with any retinoid-containing medicinal product from inception up to 19 July 2016.

**Table 1: EudraVigilance search criteria**

|                                    |                                                                                                                                |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Data quality sign-off              | 19 July 2016                                                                                                                   |
| Query time period                  | Cases with receive date until 19 July 2016                                                                                     |
| Substances                         | Single or multi-ingredient formulations of Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tretinoin, Tazarotene |
| Events of interest (MedDRA v.19.0) | Psychiatric disorders SOC                                                                                                      |

### 6.3.1. Data analysis technique

From the data extracted, analyses were run of the distribution of reports per retinoid, route of administration, reporting year (receive date), location (country), demographic characteristics (age groups, gender), medical history (history of psychiatric disorders) and duration of treatment. Where possible, correlations of the abovementioned variables were provided.

To report on relevant MedDRA PTs, PRRs were used as a disproportionality metric and were calculated for each INN and MedDRA PT.

This data was analysed cumulatively for all retinoids, stratified by individual retinoid and stratified by route of administration. Output tables were adjusted accordingly. The analysis pertaining to fatal cases resulting from self-injury was presented separately as a subgroup analysis.

As the exploratory analysis revealed thousands of case reports for the System Organ Class (SOC) Psychiatric disorders, individual case safety reviews were not produced systematically but only where the data allowed a focused discussion.

## 7. Results

### 7.1. Pooled cases

#### 7.1.1. Summary tabulations

There are 10,295 case reports of acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin-containing medicinal products and any reaction from the Psychiatric SOC in EV reported up to 19 July 2016. Of these, roughly 96% refer to psychiatric adverse reactions where isotretinoin was considered a suspect or interacting medicinal product (Table 2).

As a sensitivity analysis, we ran an extended retinoid search including retinol, etretinate and vitamin A preparations, which accounted for an additional 145 case reports in the database.

**Table 2: Distribution of case reports per International Non-proprietary Nomenclature.** The count of retinoids in the scope of the referral is the total count of cases for the list of substances in the Appendix I – INN and Scientific Composition (High Level). Also showing, for information only, the total count of cases for all other retinoids (according to ATC DDD) which were not in the scope of the referral. Count of individual INNs should not be summed, as there are cases where more than one INN was reported.

| INN                                                  | Count Cases   |
|------------------------------------------------------|---------------|
| <b><i>Retinoids in the scope of the referral</i></b> | <b>10,295</b> |
| Acitretin                                            | 123           |
| Adapalene                                            | 10            |
| Alitretinoin                                         | 225           |
| Bexarotene                                           | 14            |
| Isotretinoin                                         | 9,866         |
| Tazarotene                                           | 2             |
| Tretinoin                                            | 59            |
| <b><i>All other retinoids in EV</i></b>              | <b>145</b>    |

The oral route of administration was the most frequently reported route of administration in the case reports. Noticeably, 4,792 case reports<sup>1</sup> (46%) either had no information coded for the route of administration or were coded as route unknown.

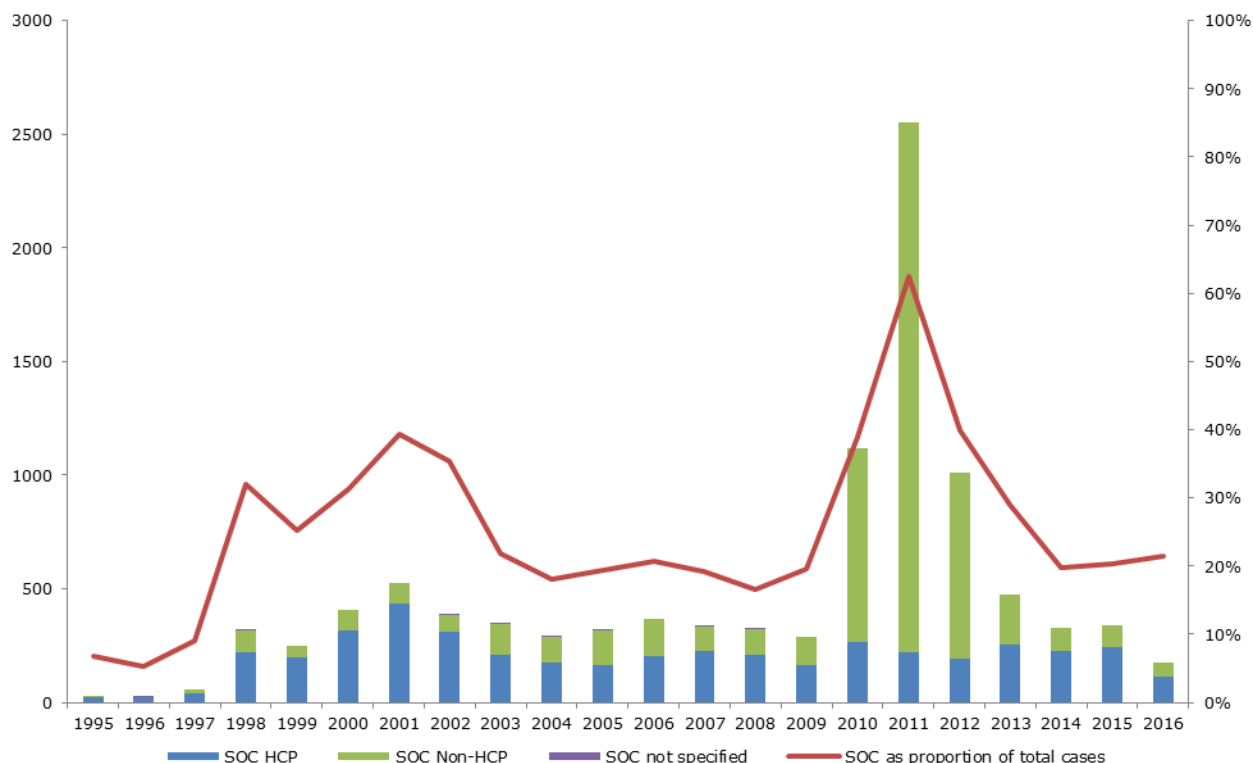
**Table 3: Distribution of case reports per administration route.** Rows should not be summed as individual case reports may have coded more than one route of administration.

| Administration Route | Count Cases |
|----------------------|-------------|
| Oral use             | 5,772       |
| Unknown use          | 4,304       |
| Not Available        | 584         |
| Topical use          | 26          |
| Transplacental use   | 10          |
| Cutaneous use        | 4           |
| Intrauterine use     | 4           |
| Other use            | 2           |
| Transdermal use      | 1           |

<sup>1</sup> The count is different to the sum of rows in Table 3 as per the reason mentioned in the table.

Concerning the distribution of case reports by primary source qualification of the reporter and by receive year, the number of reports of the Psychiatric SOC (for the retinoids in the scope of the referral) seems to have been relatively stable between 1998 and 2009, similarly, the count of cases for reports per primary source qualification was relatively consistent (Figure 1).

In the three years from 2010 to 2012, there was a large increase in the count of case reports, which seems to correlate with a substantive increase in the case reports from non-healthcare professionals. This peak returned to roughly the same 1998-2009 values from 2013 onwards.



**Figure 1: Distribution of case reports of Psychiatric SOC (total and from Non-HCP) by primary source qualification and per receive year (01/01/1995 - 19/07/2016).** Line shows the proportion of case reports of Psychiatric SOC as compared to the total count of cases for the year.

Case reports tend to refer more frequently to patients of male gender (Table 4). In all age groups, up until the 30-34 age groups, there are more reports of male patients (the difference is greater between ages 15-29). This trend inverts from the age of 35, and from then onwards female gender is always more reported, apart from the age group 75-79 which has the same counts for both genders.

**Table 4: Distribution of case reports by age group (5-year intervals) and gender.**

| Age group | Female | Male | Not Specified |
|-----------|--------|------|---------------|
| 0-4       | 8      | 17   | 1             |
| 5-9       | 3      | 6    |               |
| 10-14     | 144    | 147  | 2             |
| 15-19     | 814    | 1386 | 12            |
| 20-24     | 580    | 735  | 5             |
| 25-29     | 611    | 755  | 2             |
| 30-34     | 581    | 623  |               |

| Age group     | Female | Male | Not Specified |
|---------------|--------|------|---------------|
| 35-39         | 475    | 433  | 1             |
| 40-44         | 435    | 333  | 4             |
| 45-49         | 314    | 243  | 1             |
| 50-54         | 219    | 148  | 1             |
| 50-59         | 150    | 76   | 1             |
| 60-64         | 85     | 51   |               |
| 65-69         | 37     | 20   |               |
| 70-74         | 15     | 14   |               |
| 75-79         | 6      | 6    |               |
| 80-84         | 4      | 6    |               |
| 85+           | 5      | 1    |               |
| Not available | 283    | 281  | 215           |

Most reports are from the United States (72%) (Table 5) and the top ten countries account for 95% of the reports in EudraVigilance. In total, the EEA received 1,942 case reports (19%) of all case reports.

**Table 5: Distribution of case reports by primary source country (top 15 most frequent).**

| Primary Source Country | Count Cases | Prop. (%) |
|------------------------|-------------|-----------|
| United States          | 7,456       | 72%       |
| France                 | 624         | 6%        |
| United Kingdom         | 496         | 5%        |
| Brazil                 | 271         | 3%        |
| Germany                | 253         | 2%        |
| Australia              | 197         | 2%        |
| Canada                 | 188         | 2%        |
| Sweden                 | 124         | 1%        |
| Switzerland            | 97          | 1%        |
| Denmark                | 81          | 1%        |
| Ireland                | 80          | 1%        |
| Netherlands            | 60          | 1%        |
| Spain                  | 37          | 0%        |
| Belgium                | 33          | 0%        |

### 7.1.2. Events of interest

Depressive disorders, Suicidal, self-injurious behaviour, Anxiety symptoms and Emotional and mood disturbances NEC are the four most reported HLTs of the Psychiatric disorders SOC (Table 6).

**Table 6: Distribution of case reports by reaction at HLT level (top 20 most frequently reported HLTs).**

Rows should not be summed as individual case reports may have coded more than one reaction.

| Reaction HLT                          | Count Cases |
|---------------------------------------|-------------|
| Depressive disorders                  | 6,643       |
| Suicidal and self-injurious behaviour | 2,827       |

| Reaction HLT                                     | Count Cases |
|--------------------------------------------------|-------------|
| Anxiety symptoms                                 | 1,759       |
| Emotional and mood disturbances NEC              | 1,623       |
| Behaviour and socialisation disturbances         | 495         |
| Mood alterations with depressive symptoms        | 423         |
| Disturbances in initiating and maintaining sleep | 350         |
| Fluctuating mood symptoms                        | 339         |
| Psychotic disorder NEC                           | 281         |
| Panic attacks and disorders                      | 278         |
| Mental disorders NEC                             | 268         |
| Bipolar disorders                                | 214         |
| Abnormal behaviour NEC                           | 185         |
| Perception disturbances                          | 175         |
| Confusion and disorientation                     | 134         |
| Sleep disorders NEC                              | 125         |
| Affect alterations NEC                           | 122         |
| Mood disorders NEC                               | 115         |
| Obsessive-compulsive disorders and symptoms      | 110         |
| Eating disorders NEC                             | 86          |

There are 254 different MedDRA PTs from the Psychiatric SOC reported in association with retinoids, to focus the results we considered the PTs for the four most frequently reported HLTs (Table 7). Depression tops the list of PTs and is reported roughly 3.5 times more often than the second most reported term in the list.

**Table 7: Distribution of case reports by reaction at PT level (top 20 PTs most frequently reported in the top 4 most reported HLTs).** Rows should not be summed as individual case reports may have coded more than one reaction.

| Reaction PT             | Count Cases |
|-------------------------|-------------|
| Depression              | 6,530       |
| Suicidal ideation       | 1,853       |
| Anxiety                 | 1,309       |
| Emotional distress      | 1,038       |
| Suicide attempt         | 688         |
| Stress                  | 410         |
| Completed suicide       | 369         |
| Mood altered            | 255         |
| Irritability            | 179         |
| Anger                   | 128         |
| Major depression        | 101         |
| Agitation               | 87          |
| Emotional disorder      | 83          |
| Self-injurious ideation | 60          |
| Intentional self-injury | 58          |

| Reaction PT                    | Count Cases |
|--------------------------------|-------------|
| Nervousness                    | 41          |
| Self injurious behaviour       | 32          |
| Suicidal behaviour             | 30          |
| Depression suicidal            | 17          |
| Persistent depressive disorder | 14          |

Table 8 shows the list of PTs from the Psychiatric SOC where a disproportional PRR was identified, sorted by descending order of 95% confidence interval lower bound.

**Table 8: List of INN and reaction PT that reached the threshold for signal of disproportionality.** PRR values sorted in descending order of lower bound.

| INN          | Reaction PT                                               | Count Spontaneous | PRR (-) |
|--------------|-----------------------------------------------------------|-------------------|---------|
| Alitretonin  | Emotional poverty                                         | 3                 | 37.21   |
| Alitretonin  | Depressed mood                                            | 48                | 35.70   |
| Isotretinoin | Depression                                                | 6,177             | 18.13   |
| Alitretonin  | Mood altered                                              | 12                | 13.78   |
| Isotretinoin | Bulimia nervosa                                           | 21                | 13.61   |
| Alitretonin  | Depressive symptom                                        | 4                 | 13.59   |
| Isotretinoin | Anorexia nervosa                                          | 15                | 13.54   |
| Isotretinoin | School refusal                                            | 8                 | 13.08   |
| Isotretinoin | Social anxiety disorder                                   | 19                | 12.68   |
| Alitretonin  | Listless                                                  | 5                 | 9.93    |
| Isotretinoin | Suicidal ideation                                         | 1,564             | 9.87    |
| Isotretinoin | Emotional distress                                        | 1,037             | 9.44    |
| Alitretonin  | Decreased interest                                        | 3                 | 9.41    |
| Isotretinoin | Bipolar disorder                                          | 175               | 8.95    |
| Isotretinoin | Generalised anxiety disorder                              | 25                | 8.30    |
| Isotretinoin | Adjustment disorder with mixed anxiety and depressed mood | 4                 | 7.83    |
| Alitretonin  | Depression                                                | 60                | 7.47    |
| Isotretinoin | Brief psychotic disorder with marked stressors            | 8                 | 7.46    |
| Isotretinoin | Affect lability                                           | 99                | 7.42    |
| Isotretinoin | Stress                                                    | 405               | 7.34    |
| Isotretinoin | Adjustment disorder                                       | 21                | 7.08    |
| Isotretinoin | Mood swings                                               | 295               | 7.04    |
| Isotretinoin | Attention deficit/hyperactivity disorder                  | 59                | 6.76    |
| Isotretinoin | Major depression                                          | 94                | 6.59    |
| Alitretonin  | Loss of libido                                            | 3                 | 6.55    |
| Isotretinoin | Obsessive-compulsive disorder                             | 92                | 6.29    |
| Isotretinoin | Mood altered                                              | 196               | 6.13    |
| Alitretonin  | Tension                                                   | 3                 | 6.13    |
| Isotretinoin | Social avoidant behaviour                                 | 60                | 6.04    |
| Alitretonin  | Sleep disorder                                            | 13                | 5.54    |
| Isotretinoin | Self-injurious ideation                                   | 36                | 5.52    |
| Isotretinoin | Depressive symptom                                        | 45                | 5.41    |
| Isotretinoin | Panic attack                                              | 227               | 4.92    |
| Isotretinoin | Persistent depressive disorder                            | 13                | 4.69    |
| Isotretinoin | Postpartum depression                                     | 7                 | 4.66    |
| Isotretinoin | Morbid thoughts                                           | 13                | 4.50    |
| Isotretinoin | Dissociative identity disorder                            | 4                 | 4.35    |
| Isotretinoin | Mental disorder                                           | 241               | 4.24    |
| Alitretonin  | Thinking abnormal                                         | 4                 | 4.23    |
| Isotretinoin | Bipolar I disorder                                        | 24                | 4.22    |
| Isotretinoin | Affective disorder                                        | 43                | 4.20    |
| Alitretonin  | Suicidal ideation                                         | 18                | 4.15    |
| Isotretinoin | Post-traumatic stress disorder                            | 36                | 4.12    |
| Isotretinoin | Body dysmorphic disorder                                  | 5                 | 4.07    |
| Alitretonin  | Mood swings                                               | 6                 | 4.02    |
| Isotretinoin | Personality change                                        | 70                | 3.87    |
| Isotretinoin | Antisocial behaviour                                      | 10                | 3.83    |
| Isotretinoin | Panic disorder                                            | 34                | 3.78    |
| Isotretinoin | Suicide attempt                                           | 632               | 3.76    |
| Isotretinoin | Borderline personality disorder                           | 6                 | 3.74    |
| Isotretinoin | Personality disorder                                      | 30                | 3.71    |

| INN          | Reaction PT                              | Count Spontaneous | PRR (-) |
|--------------|------------------------------------------|-------------------|---------|
| Isotretinoin | Automatism                               | 5                 | 3.68    |
| Isotretinoin | Anxiety                                  | 1,224             | 3.44    |
| Isotretinoin | Bipolar II disorder                      | 4                 | 3.38    |
| Isotretinoin | Negative thoughts                        | 16                | 3.23    |
| Isotretinoin | Anxiety disorder                         | 29                | 3.17    |
| Isotretinoin | Schizophrenia                            | 74                | 3.12    |
| Isotretinoin | Intentional self-injury                  | 48                | 3.12    |
| Isotretinoin | Depressed mood                           | 194               | 2.87    |
| Isotretinoin | Psychotic disorder                       | 230               | 2.86    |
| Isotretinoin | Anger                                    | 109               | 2.81    |
| Isotretinoin | Violence-related symptom                 | 13                | 2.69    |
| Isotretinoin | Asocial behaviour                        | 3                 | 2.61    |
| Isotretinoin | Emotional disorder                       | 78                | 2.60    |
| Isotretinoin | Phobia                                   | 9                 | 2.60    |
| Isotretinoin | Morose                                   | 4                 | 2.42    |
| Isotretinoin | Psychotic behaviour                      | 12                | 2.36    |
| Alitretonin  | Anxiety                                  | 21                | 2.33    |
| Isotretinoin | Schizophreniform disorder                | 5                 | 2.28    |
| Isotretinoin | Feeling guilty                           | 7                 | 2.26    |
| Alitretonin  | Irritability                             | 7                 | 2.25    |
| Isotretinoin | Decreased interest                       | 20                | 2.19    |
| Isotretinoin | Paranoia                                 | 76                | 2.18    |
| Isotretinoin | Adjustment disorder with depressed mood  | 12                | 2.18    |
| Isotretinoin | Acute psychosis                          | 20                | 2.16    |
| Isotretinoin | Abnormal behaviour                       | 161               | 2.07    |
| Isotretinoin | Depression suicidal                      | 13                | 2.05    |
| Isotretinoin | Aggression                               | 217               | 2.04    |
| Isotretinoin | Completed suicide                        | 358               | 1.96    |
| Isotretinoin | Trichotillomania                         | 3                 | 1.94    |
| Isotretinoin | Suicidal behaviour                       | 24                | 1.91    |
| Isotretinoin | Feelings of worthlessness                | 6                 | 1.88    |
| Isotretinoin | Self injurious behaviour                 | 22                | 1.88    |
| Isotretinoin | Feeling of despair                       | 13                | 1.83    |
| Isotretinoin | Flat affect                              | 10                | 1.82    |
| Isotretinoin | Obsessive thoughts                       | 9                 | 1.77    |
| Isotretinoin | Agoraphobia                              | 6                 | 1.73    |
| Isotretinoin | Depersonalisation/derealisation disorder | 12                | 1.73    |
| Isotretinoin | Alcohol abuse                            | 12                | 1.68    |
| Isotretinoin | Psychiatric symptom                      | 22                | 1.65    |
| Isotretinoin | Self esteem decreased                    | 7                 | 1.62    |
| Isotretinoin | Libido decreased                         | 35                | 1.59    |
| Isotretinoin | Impulse-control disorder                 | 10                | 1.58    |
| Isotretinoin | Flight of ideas                          | 4                 | 1.57    |
| Isotretinoin | Irritability                             | 153               | 1.53    |
| Alitretonin  | Restlessness                             | 5                 | 1.47    |
| Isotretinoin | Apathy                                   | 48                | 1.44    |
| Isotretinoin | Delusion                                 | 48                | 1.38    |
| Isotretinoin | Abulia                                   | 5                 | 1.35    |
| Isotretinoin | Hallucination, auditory                  | 49                | 1.35    |
| Isotretinoin | Thinking abnormal                        | 37                | 1.31    |
| Acitretin    | Suicidal behaviour                       | 3                 | 1.31    |
| Alitretonin  | Aggression                               | 5                 | 1.28    |
| Acitretin    | Psychiatric symptom                      | 3                 | 1.26    |
| Isotretinoin | Tearfulness                              | 15                | 1.25    |
| Alitretonin  | Insomnia                                 | 10                | 1.21    |
| Isotretinoin | Selective eating disorder                | 13                | 1.17    |
| Isotretinoin | Derealisation                            | 7                 | 1.17    |
| Isotretinoin | Eating disorder                          | 33                | 1.16    |
| Isotretinoin | Loss of libido                           | 16                | 1.15    |
| Isotretinoin | Schizoaffective disorder                 | 6                 | 1.15    |
| Isotretinoin | Mania                                    | 52                | 1.12    |
| Isotretinoin | Learning disorder                        | 5                 | 1.12    |
| Alitretonin  | Agitation                                | 6                 | 1.11    |
| Alitretonin  | Mental disorder                          | 3                 | 1.09    |
| Isotretinoin | Insomnia                                 | 305               | 1.06    |
| Isotretinoin | Disturbance in sexual arousal            | 4                 | 1.02    |
| Isotretinoin | Sleep disorder                           | 97                | 1.01    |

### 7.1.3. Indications

There are 104 indications reported at MedDRA PT level in the case reports, for ease of understanding, we grouped these in logical groups (Appendix II – Group of indications). The most frequently reported group of indications was acneiform eruptions, with only marginal numbers (<5%) for all other reported indications (Table 9).

**Table 9: Distribution of case reports by group of indications.** Rows should not be summed as individual case reports may have coded more than one reaction.

| Indications                           | Count Cases |
|---------------------------------------|-------------|
| Acneiform eruptions                   | 7,888       |
| Unknown indications                   | 1,523       |
| Eczema                                | 161         |
| Other skin conditions                 | 124         |
| Psoriasis                             | 80          |
| Conditions of the skin appendages     | 64          |
| Lymphoid-related cutaneous conditions | 37          |
| Dermatitis                            | 28          |
| Other types of neoplasms              | 10          |
| Other non-skin conditions             | 9           |
| Skin neoplasms                        | 6           |
| Lichenoid eruptions                   | 5           |

### 7.1.4. Medical history

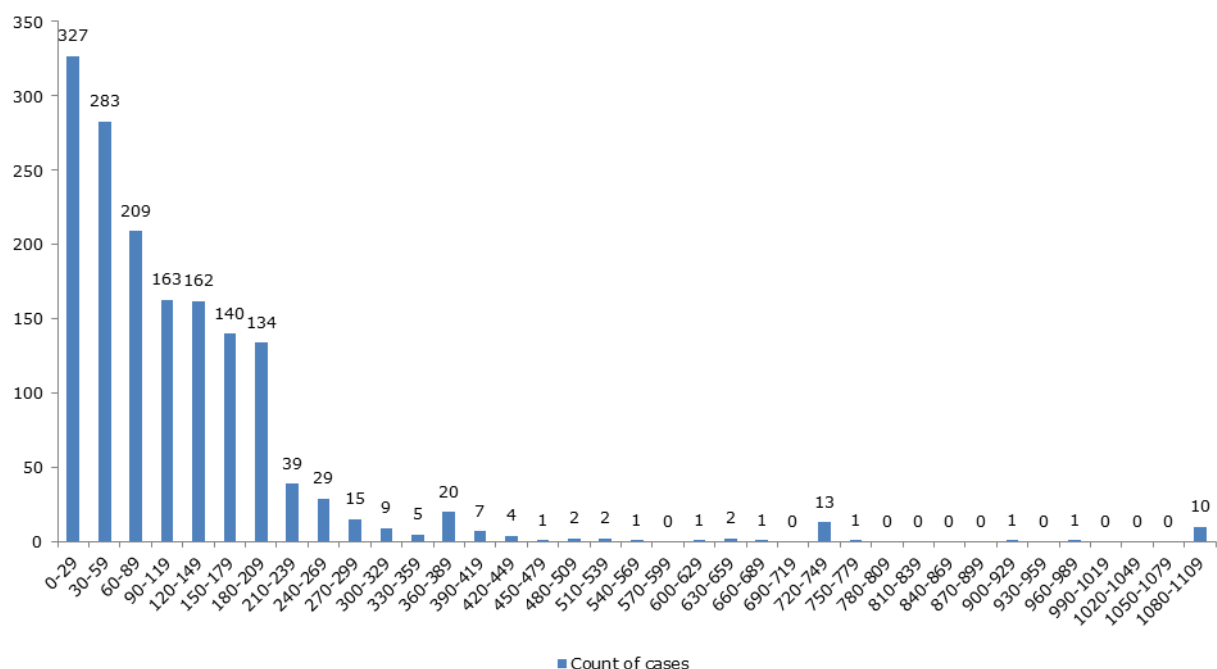
Nine-hundred and fifty six case reports (9%) have medical history of any form of depression, anxiety, suicidal ideation and suicide attempt (Table 10), most of which is depression.

**Table 10: Distribution of case reports by medical history of depression, anxiety and suicide attempt or ideation.** Rows should not be summed as individual case reports may have coded more than one medical history.

| Medical history   | Count Cases |
|-------------------|-------------|
| Depression        | 827         |
| Anxiety           | 185         |
| Suicidal ideation | 70          |
| Suicide attempt   | 36          |

### 7.1.5. Duration of treatment

The vast majority of cases of neuropsychiatric disorders report a treatment duration between 0 and 210 days (Figure 2).



**Figure 2: Distribution of case reports by reported duration of treatment (in 30 days interval).** Time-intervals are presented for the first 3 years.

## 7.2. Stratification by INN

Looking at the distribution of case reports by specific retinoid INN, the gender distribution is as presented in Table 11.

**Table 11: Distribution of case reports by gender and INN**

| INN          | Female | Male  | Not Specified |
|--------------|--------|-------|---------------|
| Acitretin    | 65     | 57    | 1             |
| Adapalene    | 8      | 2     |               |
| Alitretonin  | 133    | 77    | 15            |
| Bexarotene   | 4      | 10    |               |
| Isotretinoin | 4,524  | 5,117 | 225           |
| Tazarotene   | 2      |       |               |
| Tretinoin    | 35     | 19    | 5             |

Interestingly, the age distribution per INN (Table 12) shows that for isotretinoin, there is a peak reporting frequency at the age of 15-19, whereas for alitretonin that occurs later on from the age of 40. This could reflect use patterns or be a chance finding considering that the number of observations for alitretonin are small.

**Table 12: Distribution of case reports by age groups and INN.**

| Age Year      | Acitretin | Adapalene | Alitretinoin | Bexarotene | Isotretinoin | Tazarotene | Tretinoin |
|---------------|-----------|-----------|--------------|------------|--------------|------------|-----------|
| 0-4           |           |           |              |            | 21           |            | 5         |
| 5-9           | 1         |           |              |            | 8            |            |           |
| 10-14         |           | 2         |              |            | 291          |            |           |
| 15-19         | 5         | 2         | 1            |            | 2,203        |            | 1         |
| 20-24         |           | 1         | 4            |            | 1,313        |            | 2         |
| 25-29         | 9         |           | 8            |            | 1,347        |            | 5         |
| 30-34         | 5         |           | 19           |            | 1,174        |            | 6         |
| 35-39         | 12        |           | 14           | 1          | 877          |            | 5         |
| 40-44         | 16        | 1         | 23           | 1          | 727          |            | 4         |
| 45-49         | 13        |           | 22           |            | 518          |            | 5         |
| 50-54         | 15        | 1         | 27           | 1          | 318          | 1          | 6         |
| 55-59         | 14        |           | 25           | 1          | 184          |            | 3         |
| 60-64         | 7         |           | 16           | 4          | 107          |            | 2         |
| 65-69         | 3         |           | 8            | 2          | 41           |            | 3         |
| 70-74         | 3         |           | 10           | 3          | 11           |            | 2         |
| 75-79         | 1         |           | 4            |            | 6            |            | 1         |
| 80-84         | 3         |           | 2            |            | 4            |            | 1         |
| 85+           | 5         |           |              |            | 1            |            |           |
| Not available | 11        | 3         | 42           | 1          | 715          | 1          | 8         |

Table 13 shows the distribution of case reports by reaction at HLT level.

**Table 13: Distribution of case reports by reaction at HLT level (top 20 most frequently reported HLTs) and by INN.** Rows are sorted in descending order by total count for all INNs. Rows should not be summed as individual case reports may have coded more than one reaction.

| Reaction HLT                                     | Acitretin | Adapalene | Alitretinoin | Bexarotene | Isotretinoin | Tazarotene | Tretinoin |
|--------------------------------------------------|-----------|-----------|--------------|------------|--------------|------------|-----------|
| Depressive disorders                             | 44        | 6         | 80           | 4          | 6,503        | 1          | 7         |
| Suicidal and self-injurious behaviour            | 25        |           | 24           | 1          | 2,768        | 1          | 9         |
| Anxiety symptoms                                 | 17        | 3         | 45           | 3          | 1,685        |            | 7         |
| Emotional and mood disturbances NEC              | 4         | 2         | 28           |            | 1,583        |            | 6         |
| Behaviour and socialisation disturbances         | 8         | 1         | 13           | 1          | 469          |            | 3         |
| Mood alterations with depressive symptoms        | 5         |           | 64           | 1          | 348          | 1          | 4         |
| Disturbances in initiating and maintaining sleep | 6         | 1         | 15           | 3          | 316          |            | 10        |
| Fluctuating mood symptoms                        | 4         |           | 9            |            | 326          |            |           |
| Psychotic disorder NEC                           | 4         | 1         | 3            |            | 271          |            | 2         |
| Panic attacks and disorders                      | 4         | 1         | 2            |            | 271          |            | 1         |

| Reaction HLT                                | Acitretin | Adapalene | Alitretinoin | Bexarotene | Isotretinoin | Tazarotene | Tretinoin |
|---------------------------------------------|-----------|-----------|--------------|------------|--------------|------------|-----------|
| Mental disorders NEC                        | 3         |           | 4            | 1          | 257          |            | 3         |
| Bipolar disorders                           | 1         |           | 1            |            | 211          |            | 1         |
| Abnormal behaviour NEC                      | 7         |           | 2            |            | 171          |            | 5         |
| Perception disturbances                     | 7         |           | 4            | 1          | 160          |            | 3         |
| Confusion and disorientation                | 14        |           | 3            | 4          | 104          |            | 9         |
| Sleep disorders NEC                         | 1         | 2         | 20           | 1          | 101          |            |           |
| Affect alterations NEC                      | 1         |           | 2            |            | 119          |            |           |
| Mood disorders NEC                          |           |           | 8            | 1          | 103          |            | 3         |
| Obsessive-compulsive disorders and symptoms |           |           |              |            | 110          |            |           |

### 7.3. Stratification by route of administration

There are several routes of administration as mentioned in Table 3. We grouped those routes of administration into the main routes for retinoids: oral and dermal. As expected, the oral formulations of retinoids are the most frequently reported route, with only a marginal number of dermal use (Table 14).

**Table 14: Distribution of case reports by routes of administration.**

| Administration Route | Count Cases |
|----------------------|-------------|
| Oral                 | 5,772       |
| Dermal               | 31          |
| All others           | 16          |
| Unknown/not reported | 4,792       |

As the systemic absorption of topical retinoids seems to be slow and small<sup>2</sup>, it is important to consider the cases of neuropsychiatric reactions to dermal routes of administration carefully. From the line listing of case reports (Table 15), three case reports mention the use of antidepressants and two mention pregnancy or exposure during pregnancy. There are three case reports where suicide or suicide attempt alone were reported with no additional information on the reaction.

**Table 15: Line listing of case reports exposed to retinoids via dermal routes of administration.**

| Safety Report ID | Primary Group Qualification | Year and country | Age/ Gender | Drug list                                                                                                                        | Reaction List                                       |
|------------------|-----------------------------|------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| 13213            | Only Patient                | 2003/US          | 18/M        | Accutane [isotretinoin] (s - acne cystic - 15/06/1972 - 121 d)<br>Accutane [isotretinoin] (s - acne cystic - 15/06/1972 - 121 d) | Altered mood, Anxiety attack, Depression, Skin loss |

<sup>2</sup> Schaefer H. Penetration and percutaneous absorption of topical retinoids. A review. Skin Pharmacol. 1993;6 Suppl 1:17-23. Review. PubMed PMID: 8142107.

| Safety Report ID | Primary Group Qualification | Year and country | Age/ Gender | Drug list                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Reaction List                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------|-----------------------------|------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 374309           | Only HCP                    | 2006/CH          | 40/F        | Differin [adapalene] (s - n/a - n/a - n/a)<br>Venlafaxine [venlafaxine] (c - depression - n/a - n/a)                                                                                                                                                                                                                                                                                                                                                                         | Depression aggravated, Nose bleed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 393942           | Only Patient                | 2006/AU          | 29/F        | Roaccutane gel [isotretinoin] (s - product used for unknown indication - 01/01/1993 - 731 d)                                                                                                                                                                                                                                                                                                                                                                                 | Suicide attempt                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 1576696          | Only Patient                | 1997/US          | 62/F        | Nortriptyline hcl [nortriptyline] (c - n/a - n/a - n/a)<br>Renova [tretinoin] (s - skin dystrophy - 15/08/1996 - n/a)<br>Renova [tretinoin] (s - n/a - 15/08/1996 - n/a)                                                                                                                                                                                                                                                                                                     | Breast cancer, Burning sensation, Irritability, Redness                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 1587080          | Only Patient                | 2003/US          | ?/F         | Psychiatric drugs (nos)(qi) (c - n/a - n/a - n/a)<br>Retin-a [tretinoin] (s - product used for unknown indication - n/a - n/a)                                                                                                                                                                                                                                                                                                                                               | Asocial behavior, Burn, Hair growth increased, Photosensitive reaction, Suicidal ideation, Wrinkles                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 1607193          | Only HCP                    | 1996/US          | 32/M        | Erythromycin topical solution [erythromycin] (c - n/a - n/a - n/a)<br>Retin-a [tretinoin] (s - acne - 30/06/1996 - n/a)                                                                                                                                                                                                                                                                                                                                                      | Anxiety, Chapped skin, Cheilosis, Depression, Emotional distress, Eye swelling, Irritability, Laceration, Pain, Rash, Redness, Unevaluable event                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1614639          | Only Patient                | 2000/US          | 43/F        | Anti-depressant (c - depression - n/a - n/a)<br>Cortaid [hydrocortisone acetate] (c - n/a - n/a - n/a)<br>Renova [tretinoin] (s - ephelides - n/a - n/a)<br>Renova [tretinoin] (s - therapeutic skin care topical - n/a - n/a)                                                                                                                                                                                                                                               | Abnormal physical sensation, Anemia, Bacterial infection, Blepharoconjunctivitis, Blisters, Blurred vision, Bone injury, Chemical burns of eye, Diabetes, Dry eyes, Dry mouth, Eye infection, Eyelid margin crusting, Facial swelling, Fever, Foreign body in eye, Gastric disorder, Hemorrhage, Injury, Injury to teeth, Lung disorder, Mental disorder NOS, Migraine, Opacity corneal, Pain, Paranoid delusions, Peeling, Rhinitis, Scab, Scarring, Silicosis, Sinusitis, Skin breakdown, Sleep loss, Sores gum, Sores lip, Swelling of eyelid, Swelling of limbs, Swollen eyes, Unilateral vision loss, Vision abnormal, Weight loss, Welts, Worms |
| 1616634          | Only Patient                | 1997/US          | 29/F        | Acetaminophen, codeine [codeine, paracetamol] (c - n/a - 15/03/1997 - n/a)<br>Mineral supplement (c - n/a - n/a - n/a)<br>Multivitamins with vitamin a [ascorbic acid, ergocalciferol, folic acid, nicotinamide, panthenol, retinol, riboflavin, thiamine hydrochloride] (c - n/a - n/a - n/a)<br>Retin-a [tretinoin] (s - acne - 01/07/1996 - n/a)<br>Retin-a [tretinoin] (s - acne - 01/07/1997 - n/a)<br>Retin-a [tretinoin] (s - scar - 01/07/1996 - n/a)                | <b>Drug exposure during pregnancy,</b> Fatigue, Gastric disorder, Insomnia, Irritability, Joint pain, Migraine, Miscarriage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 1939739          | Only HCP                    | 1997/FR          | 20/F        | 1 concomitant drug [generic component(s) unknown(qi)] (c - n/a - n/a - n/a)<br>Diane 35 [cyproterone] (c - contraception - n/a - n/a)<br>Diane 35 [ethinylestradiol] (c - contraception - n/a - n/a)<br>Eclaran [benzoyl peroxide] (c - n/a - n/a - n/a)<br>Eryfluid [erythromycin] (c - n/a - n/a - n/a)<br>Roaccutane gel [isotretinoin] (s - acne - 15/04/1994 - n/a)<br>Roaccutane [isotretinoin] (s - acne - 15/01/1993 - n/a)<br>Roaccutane [isotretinoin] (s - acne - | Influenza like illness, Allergic reaction, Headache, Quincke's oedema, Insomnia, Back pain, Myalgia, Mycoplasma infection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| Safety Report ID | Primary Group Qualification    | Year and country | Age/ Gender | Drug list                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Reaction List                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------|--------------------------------|------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  |                                |                  |             | 15/03/1994 - 3 d)<br>Roaccutane [isotretinoin] (s - acne - 15/10/1993 - n/a)<br>Roaccutane [isotretinoin] (s - acne - 15/11/1993 - 5 d)                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 1962197          | Patient + Others (HCP / Legal) | 1998/US          | 29/F        | Accutane capsules [isotretinoin] (s - acne - 01/07/1983 - 60 d)<br>Accutane capsules [isotretinoin] (s - acne - 01/07/1992 - 152 d)<br>Accutane capsules [isotretinoin] (s - acne - 15/03/1997 - n/a)<br>Accutane capsules [isotretinoin] (s - acne - 15/10/1997 - n/a)<br>Retin a [tretinoin] (s - scar - 02/11/1997 - n/a)<br>Retin a [tretinoin] (s - scar - 22/01/1998 - n/a)<br>Vitamin a [retinol] (c - n/a - 24/12/1997 - n/a)<br>Vitamin b [vitamin b complex] (c - n/a - 24/12/1997 - n/a)<br>Vitamin e [vitamin e] (c - n/a - 24/12/1997 - n/a) | Anxiety, Diabetes, Dizziness, Exhaustion, Fainting, Fever, Headache, Hyperactivity, Hypoglycaemia, Insomnia, Menstrual disorder NOS, Nausea, Nosebleed, Panic attack, Seizure, Shaking                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 1978608          | Only Patient                   | 2006/CH          | ?/M         | Roaccutan [isotretinoin] (s - acne - n/a - n/a)<br>Roaccutan [isotretinoin] (s - acne - n/a - n/a)                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Suicide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 2119233          | Patient + Others (HCP / Legal) | 2000/US          | 51/F        | Anti-depressant (c - depression - n/a - n/a)<br>Cortaid [hydrocortisone acetate] (c - n/a - n/a - n/a)<br>Renova [tretinoin] (s - ephelides - n/a - n/a)<br>Renova [tretinoin] (s - therapeutic skin care topical - n/a - n/a)                                                                                                                                                                                                                                                                                                                            | Anemia, Neuropathy peripheral, Skin disorder, Sores lip, Abnormal physical sensation, Epstein-Barr virus infection, Injury to teeth, Migraine, Pain, Swallowing difficult, Bacterial infection, Dry eyes, Lung disorder, Paranoid delusions, Scab, Sinusitis, Sleep loss, Swollen ankles, Vision abnormal, Welts, Sores gum, Chemical burns of eye, Hemorrhage, Nasal sinus congestion, Peeling, Scarring, Weight loss, Blurred vision, Fever, Joint pain, Mental disorder NOS, Gastric disorder, Burning skin, Diabetes, Diarrhea, Dry mouth, Facial swelling, Silicosis, Swelling of limbs, Swollen eyes, Skin breakdown, Eyelid margin crusting, Unilateral vision loss, Blisters, Eye infection, Foreign body in eye, Injury, Leukocytodastic vasculitis, Opacity corneal, Palpitations, Rhinitis, Bone injury, Worms, Blepharoconjunctivitis, Cough, Swelling of eyelid |
| 2306161          | Only HCP                       | 2008/US          | ?/?         | Cleocin (c - acne - 26/02/2008 - n/a)<br>Doxycycline (c - acne - 15/04/2008 - n/a)<br>Isotretinoin (s - product used for unknown indication - 29/05/2008 - 15 d)<br>Isotretinoin (s - n/a - 07/08/2007 - 204 d)<br>Minocycline (c - acne - 12/06/2008 - n/a)<br>Retin-a (s - acne - 26/02/2008 - n/a)                                                                                                                                                                                                                                                     | Depression, <b>Pregnancy</b> , Treatment noncompliance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 3380927          | Only HCP                       | 2009/CA          | 16/M        | Clindoxyl [benzoyl peroxide, clindamycin phosphate] (c - acne - n/a - n/a)<br>Differin xp [adapalene] (s - n/a - 01/07/2008 - n/a)                                                                                                                                                                                                                                                                                                                                                                                                                        | Attention concentration difficulty, Altered mood, Anxiety, Sleep disturbance, Depressed state                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 3614338          | Only Patient                   | 2007/BR          | 38/F        | Glycerin [glycerin] (c - n/a - n/a - n/a)<br>Isotrex cream [isotretinoin] (s - pigmentation disorder - 18/01/2007 - n/a)<br>Sundown [octinoxate, octylsalicylate,                                                                                                                                                                                                                                                                                                                                                                                         | Depression, Erythema, Burning sensation, Swelling, Candidiasis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| Safety Report ID | Primary Group Qualification | Year and country | Age/ Gender | Drug list                                                                                                                                                                                                                                                                                                                                                                    | Reaction List                                                                                                                                                                                                                                   |
|------------------|-----------------------------|------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  |                             |                  |             | oxybenzone, titanium dioxide] (c - n/a - n/a - n/a)                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                 |
| 3614615          | Only HCP                    | 1999/UK          | 15/F        | Isotrexin [erythromycin, isotretinoin] (s - acne - 28/09/1998 - 42 d)                                                                                                                                                                                                                                                                                                        | Depression, Emotional instability                                                                                                                                                                                                               |
| 3856429          | Only HCP                    | 2010/US          | ?/F         | Differin [adapalene] (s - acne - 14/10/2001 - n/a)                                                                                                                                                                                                                                                                                                                           | Depression                                                                                                                                                                                                                                      |
| 4515496          | Only HCP                    | 1994/US          | 39/F        | Cyclobenzaprine hydrochloride [cyclobenzaprine hydrochloride] (s - product used for unknown indication - n/a - n/a)<br>Doxepin hydrochloride [doxepin hydrochloride] (s - product used for unknown indication - n/a - n/a)<br>Retin-a [tretinoin] (s - acne - 01/07/1993 - n/a)<br>Retin-a [tretinoin] (s - acne - n/a - n/a)                                                | Ataxia, Itching, Excoriation, Anxiety, Headache, Memory loss, Toxic encephalopathy, Depression worsened, Dysarthria, Hepatitis, Intentional misuse, Overdose                                                                                    |
| 5421790          | Only HCP                    | 2005/US          | 75/M        | Solage (s - skin hyperpigmentation - 15/02/2004 - n/a)                                                                                                                                                                                                                                                                                                                       | Emotional disturbance NOS, Vitiligo                                                                                                                                                                                                             |
| 6285859          | Only Patient                | 2013/AU          | 14/M        | Epiduo [adapalene 0.1% / benzoyl peroxide 2.5% gel, adapalene, benzoyl peroxide] (s - acne - n/a - n/a)                                                                                                                                                                                                                                                                      | Chemical burn, Expressive language disorder, Difficulty breathing, Blister, Swelling face, Eating disorder                                                                                                                                      |
| 6315754          | Only HCP                    | 2013/NL          | 19/F        | Tretinoine creme 0,2mg/g [tretinoine] (s - acne - 01/07/2012 - n/a)                                                                                                                                                                                                                                                                                                          | Psychic disturbance                                                                                                                                                                                                                             |
| 6473415          | Only Patient                | 2011/CA          | ?/F         | Differin [adapalene] (s - n/a - 15/08/2009 - n/a)<br>Differin [adapalene] (s - n/a - 15/09/2008 - n/a)                                                                                                                                                                                                                                                                       | Rash NOS, Rash papular, Nausea, Depression, Stress, Dry skin, Redness, Skin irritation, Hair loss, Acne aggravated, Skin burning sensation, Skin scarring, Skin infection NOS, Dizziness, Bruising, Yeast infection, Gingival hyperpigmentation |
| 7149547          | Only HCP                    | 2010/FR          | 28/M        | Curacne [isotretinoin] (s - acne - 15/11/2008 - n/a)<br>Zyprexa [olanzapine] (c - schizophrenia - n/a - n/a)                                                                                                                                                                                                                                                                 | Suicide                                                                                                                                                                                                                                         |
| 7585894          | Only Patient                | 2013/US          | 34/M        | Ziana [clindamycin phosphate, tretinoin] (s - acne - 15/02/2013 - n/a)                                                                                                                                                                                                                                                                                                       | Suicidal ideation, Rosacea                                                                                                                                                                                                                      |
| 8396104          | Only Patient                | 2014/US          | 41/F        | Benzoyl peroxide/clindamycin [benzoyl peroxide, clindamycin] (s - rosacea - 08/05/2014 - n/a)<br>Tretinoin [liposomal tretinoin, tretinoin] (s - rosacea - 08/05/2014 - n/a)<br>Tretinoin [liposomal tretinoin, tretinoin] (s - scar - 08/05/2014 - n/a)<br>Finacea [azelaic acid] (c - n/a - n/a - n/a)<br>Hydroquinone [hydroquinone] (c - n/a - n/a - n/a)                | Difficulty sleeping, Skin discoloration, Application site exfoliation, Itching, Allergic reaction, Rash, Eyes swollen, Skin rough, Face red, Facial swelling, Application site burning, Off label use, Sun sensitivity                          |
| 9192082          | Only Patient                | 2015/SE          | 20/F        | Epiduo [adapalene, benzoyl peroxide] (s - acne - 01/01/2015 - n/a)                                                                                                                                                                                                                                                                                                           | Dry skin, Sleep disorder, Erythema, Chemical burn, Pain of skin, Skin hyperpigmentation, Itching, Flaking skin, Allergic contact dermatitis                                                                                                     |
| 9433933          | Only HCP                    | 2015/UK          | ?/F         | Roaccutane [isotretinoin] (s - acne - n/a - n/a)                                                                                                                                                                                                                                                                                                                             | Sleep disturbance                                                                                                                                                                                                                               |
| 9667248          | Only Patient                | 2015/US          | 13/F        | Epiduo (adapalene, benzoyl peroxide) gel 0.1% / 2.5% [adapalene, benzoyl peroxide] (s - acne - 19/07/2015 - n/a)<br>Epiduo (adapalene, benzoyl peroxide) gel 0.1% / 2.5% [adapalene, benzoyl peroxide] (s - n/a - n/a - n/a)<br>Minocycline [minocycline] (c - acne - n/a - 240 d)<br>Preprepared face cloths from cvs(qi) (c - therapeutic skin care topical - n/a - 365 d) | Breathing difficult, Allergic reaction, Stomach pain, Accidental ingestion of drug, Itching mouth, Itching all over, Urticaria, Burning mouth, Itchy throat, Anxiety attack, Lip swelling                                                       |
| 9797865          | Only HCP                    | 2015/US          | 54/F        | Interleukin-2 [aldesleukin] (s - metastatic malignant melanoma -                                                                                                                                                                                                                                                                                                             | Depression worsened, Nausea, Malignant neoplasm progression,                                                                                                                                                                                    |

| Safety Report ID | Primary Group Qualification    | Year and country | Age/ Gender | Drug list                                                                                                                                                                   | Reaction List                                                    |
|------------------|--------------------------------|------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
|                  |                                |                  |             | 15/07/2014 - 7 d)<br>[imiquimod] (s - metastatic malignant melanoma - n/a - n/a)<br>[tazarotene] (s - metastatic malignant melanoma - n/a - n/a)                            | Metastatic melanoma                                              |
| 10072749         | Patient + Others (HCP / Legal) | 2015/US          | ?/F         | Aczone [dapson] (s - product used for unknown indication - 15/06/2015 - n/a)<br>Tazoraccream 0.1% [tazarotene] (s - product used for unknown indication - 15/06/2015 - n/a) | Feeling of despair, Suicidal ideation                            |
| 10515180         | Only HCP                       | 2016/US          | ?/F         | Epiduo (adapalene, benzoyl peroxide) gel 0.1% / 2.5% [adapalene, benzoyl peroxide] (s - n/a - n/a - 30 d)                                                                   | Eating disorder, Pain of skin, Swelling face, Cellulitis of face |

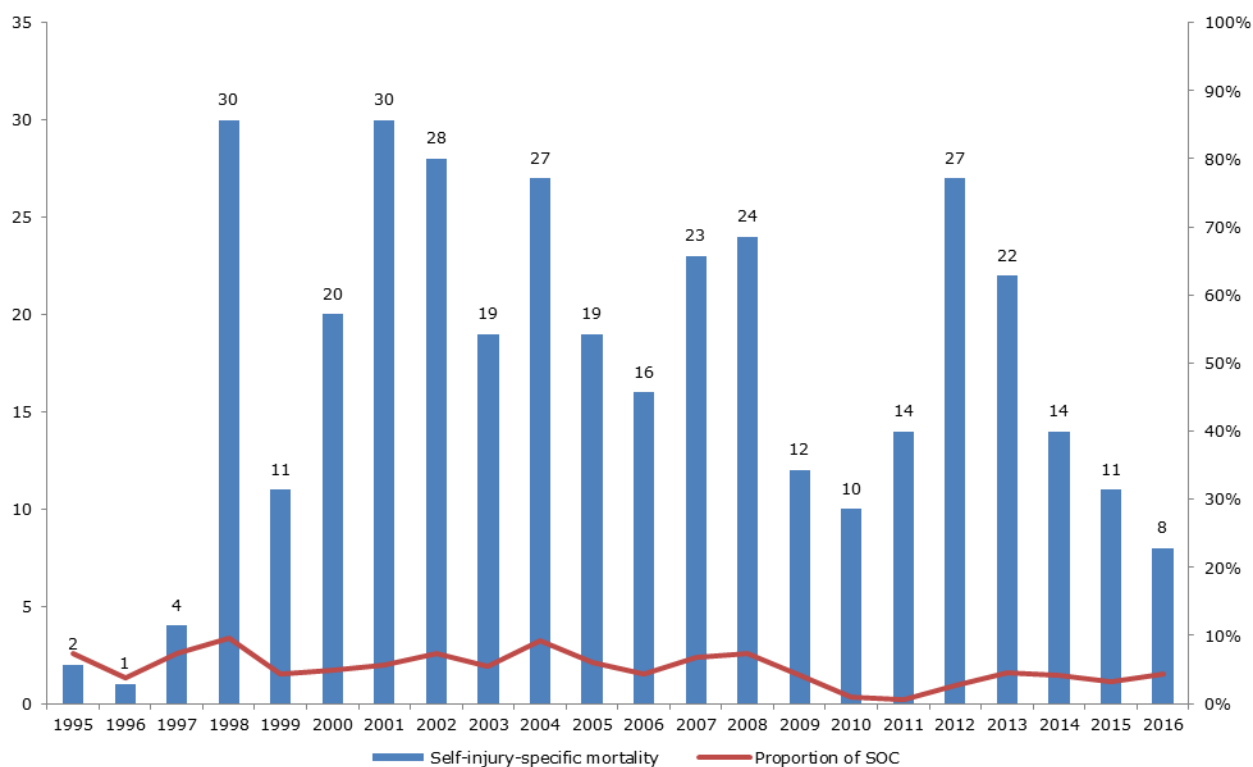
#### 7.4. Subgrouping by self-injury-specific mortality

There are 373 case reports of self-injury-specific mortality as per the definition used in 6.1.2. the vast majority of which are to isotretinoin.

**Table 16: Distribution of case reports of self-injury-specific mortality per International Non-proprietary Nomenclature.** Rows should not be summed as individual case reports may have coded more than one substance.

| INN          | Count Cases |
|--------------|-------------|
| Acitretin    | 4           |
| Adapalene    | 0           |
| Alitretinoin | 3           |
| Bexarotene   | 0           |
| Isotretinoin | 367         |
| Tazarotene   | 0           |
| Tretinoin    | 0           |

As can be seen in Figure 3, the count of case reports has been reducing since 2012, however the proportion of self-injury-specific mortality within the Psychiatric SOC has been reasonably stable as a result of an overall reduction in the total number of case reports.



**Figure 3: Distribution of case reports of self-injury-specific mortality per receive year (01/01/1995 - 19/07/2016).**

Whereas in the age distribution of psychiatric disorders the count of cases by gender was higher for males only until the age of 30-34, in the self-injury-specific mortality case reports, the frequency of reports was higher for males in all age groups up to 60 (highest for males in the age group 15-24).

**Table 17: Distribution of case reports of self-injury-specific mortality by age group (5-year intervals) and gender.**

| Age Year | Female | Male | Not Specified |
|----------|--------|------|---------------|
| 0-4      |        |      |               |
| 5-9      |        |      |               |
| 10-14    | 5      | 9    |               |
| 15-19    | 19     | 109  | 1             |
| 20-24    | 15     | 88   | 2             |
| 25-29    | 14     | 20   |               |
| 30-34    | 6      | 9    |               |
| 35-39    | 3      | 5    |               |
| 40-44    | 2      | 3    |               |
| 45-49    |        | 2    |               |
| 50-54    | 1      | 2    |               |
| 55-59    |        |      |               |
| 60-64    | 1      | 1    |               |
| 65-69    | 1      |      |               |
| 70-74    |        |      |               |

| Age Year | Female | Male | Not Specified |
|----------|--------|------|---------------|
| 75-79    |        |      |               |
| 80-84    |        |      |               |
| 85+      |        |      |               |
| N/A      | 4      | 40   | 11            |

The highest number of case reports for self-injury specific mortality is from the United States, though the proportion of the mortality cases from this country is much reduced as compared to the proportion for Psychiatric disorders.

**Table 18: Distribution of case reports of self-injury-specific mortality by primary source country (top 15 most frequent).**

| Primary Source Country | Count Cases |
|------------------------|-------------|
| United States          | 146         |
| United Kingdom         | 67          |
| France                 | 43          |
| Australia              | 25          |
| Canada                 | 13          |
| Switzerland            | 12          |
| Germany                | 10          |
| Brazil                 | 9           |
| Sweden                 | 8           |
| New Zealand            | 7           |
| Finland                | 4           |
| Iran                   | 4           |
| Denmark                | 3           |
| Belgium                | 2           |
| Colombia               | 2           |

Within the subgroup of self-injury-specific mortality, 43 case reports (12%) have medical history of any form of depression, anxiety, suicidal ideation and suicide attempt (Table 10).

**Table 19: Distribution of case reports by medical history of depression, anxiety and suicide attempt or ideation.** Rows should not be summed as individual case reports may have coded more than one medical history.

| Medical history   | Count Cases |
|-------------------|-------------|
| Depression        | 35          |
| Anxiety           | 8           |
| Suicidal ideation | 7           |
| Suicide attempt   | 3           |

## 8. Appendix I – INN and Scientific Composition (High Level)

| INN          | Scientific Composition (High Level) | Count Cases |
|--------------|-------------------------------------|-------------|
| Acitretin    | ACITRETIN                           | 123         |
| Adapalene    | ADAPALENE                           | 5           |
|              | ADAPALENE, BENZOYL PEROXIDE         | 5           |
| Alitretinoin | ALITRETINOIN                        | 225         |
| Bexarotene   | BEXAROTENE                          | 14          |
| Isotretinoin | ERYTHROMYCIN, ISOTRETINOIN          | 2           |
|              | ISOTRETINOIN                        | 9,864       |
| Tazarotene   | TAZAROTENE                          | 2           |
| Tretinoin    | CLINDAMYCIN PHOSPHATE, TRETINOIN    | 1           |
|              | ERYTHROMYCIN, TRETINOIN             | 1           |
|              | MEQUINOL, TRETINOIN                 | 1           |
|              | TRETINOIN                           | 56          |

## 9. Appendix II – Group of indications

| Group of indications                  | Indication PT                                 |
|---------------------------------------|-----------------------------------------------|
| Acneiform eruptions                   | Acne                                          |
|                                       | Acne conglobata                               |
|                                       | Acne cystic                                   |
|                                       | Acne fulminans                                |
|                                       | Acne infantile                                |
|                                       | Acne pustular                                 |
|                                       | Acne varioliformis                            |
|                                       | Oil acne                                      |
|                                       | Rosacea                                       |
| Conditions of the skin appendages     | Alopecia scarring                             |
|                                       | Folliculitis                                  |
|                                       | Hidradenitis                                  |
|                                       | Keratosis follicular                          |
| Dermatitis                            | Dermatitis                                    |
|                                       | Dermatitis acneiform                          |
|                                       | Dermatitis allergic                           |
|                                       | Dermatitis atopic                             |
|                                       | Dermatitis contact                            |
|                                       | Dermatitis papillaris capilliti               |
|                                       | Hand dermatitis                               |
|                                       | Seborrhoeic dermatitis                        |
|                                       | Dyshidrotic eczema                            |
| Eczema                                | Eczema                                        |
|                                       | Eczema asteatotic                             |
|                                       | Lichen planus                                 |
| Lichenoid eruptions                   | Lichen sclerosus                              |
|                                       | Neurodermatitis                               |
|                                       | Pityriasis lichenoides et varioliformis acuta |
|                                       | Acute lymphocytic leukaemia                   |
| Lymphoid-related cutaneous conditions | Acute myeloid leukaemia                       |
|                                       | Acute promyelocytic leukaemia                 |
|                                       | Lymphocytic infiltration                      |
|                                       | Lymphoma                                      |
|                                       | Mycosis fungoides                             |
|                                       | Chronic hepatitis C                           |
| Other non-skin conditions             | Depression                                    |
|                                       | Emphysema                                     |
|                                       | Foetal exposure during pregnancy              |
|                                       | Hepatitis C                                   |
|                                       | Keratitis                                     |
|                                       | Muscle spasticity                             |
|                                       | Retinal detachment                            |
|                                       | Cellulitis                                    |
| Other skin conditions                 | Cheilitis granulomatosa                       |
|                                       | Cutaneous lupus erythematosus                 |
|                                       | Cyst                                          |
|                                       | Dermal cyst                                   |
|                                       | Dermatomyositis                               |
|                                       | Dermatosis                                    |
|                                       | Ephelides                                     |
|                                       | Face oedema                                   |
|                                       | Furuncle                                      |
|                                       | Hyperkeratosis                                |
|                                       | Ichthyosis                                    |
|                                       | Keratoacanthoma                               |
|                                       | Mucosal inflammation                          |
|                                       | Nodule                                        |
|                                       | Palmar-plantar erythrodysesthesia syndrome    |
|                                       | Papule                                        |
|                                       | Pigmentation disorder                         |
|                                       | Pityriasis rosea                              |
|                                       | Pityriasis rubra pilaris                      |
|                                       | Pruritus                                      |
|                                       | Pulpitis dental                               |
|                                       | Rash                                          |
|                                       | Rash papular                                  |
|                                       | Rash pustular                                 |

| Group of indications    | Indication PT                            |
|-------------------------|------------------------------------------|
|                         | Scar                                     |
|                         | Scleroderma                              |
|                         | Sebaceous gland disorder                 |
|                         | Sebaceous glands overactivity            |
|                         | Sebaceous hyperplasia                    |
|                         | Seborrhoea                               |
|                         | Skin disorder                            |
|                         | Skin dystrophy                           |
|                         | Skin hyperpigmentation                   |
|                         | Skin lesion                              |
|                         | Skin mass                                |
|                         | Skin papilloma                           |
|                         | Skin reaction                            |
|                         | Skin ulcer                               |
|                         | Subcutaneous abscess                     |
|                         | Therapeutic skin care topical            |
|                         | Thermal burn                             |
|                         | Urticaria                                |
| Other types of neoplasm | Atypical teratoid/rhabdoid tumour of CNS |
|                         | Brain neoplasm                           |
|                         | Brain neoplasm malignant                 |
|                         | Lung neoplasm malignant                  |
|                         | Neoplasm malignant                       |
|                         | Neuroblastoma                            |
|                         | Non-small cell lung cancer               |
|                         | Pinealoblastoma                          |
|                         | Renal cancer                             |
| Psoriasis               | Psoriasis                                |
| Skin neoplasms          | Pustular psoriasis                       |
|                         | Basal cell carcinoma                     |
|                         | Lip and/or oral cavity cancer            |
|                         | Metastatic malignant melanoma            |
|                         | Skin cancer metastatic                   |
|                         | Squamous cell carcinoma                  |
| Unknown indication      | Off label use                            |
|                         | Product used for unknown indication      |
|                         | Unevaluable event                        |