# Supplementary Material

***Supplementary Table 1 – Data captured in the data collection spreadsheet***

|  |  |  |  |
| --- | --- | --- | --- |
| **Data element** | **Description (indication if copied from source or derived)** | **Source** | **Categories** |
| EU PAS Register number | Copied | EU PAS Register | Not applicable |
| MDS/Non-MDS | Copied | Sultana et al dataset1 (with additional validation on MDS definition) | MDS |
| Non-MDS (Primary data collection; Secondary data collection [chart review]; Secondary data collection [claims database]; Secondary data collection [electronic health record]; Secondary data collection [existing registry]) |
| Date of Final Study Report | Copied | EU PAS Register | 2012-2014; 2015-2017; 2018-2020 |
| Study title | Copied | EU PAS Register | Not applicable |
| Study type | Copied | EU PAS Register | Active surveillance; Observational Study; Other |
| Brief Description of the Study | Copied | EU PAS Register | Not applicable |
| Is the study required by a Risk Management Plan (RMP)? | Copied | EU PAS Register | EU RMP category 1 (imposed as condition of marketing authorisation); EU RMP category 2 (specific obligation of marketing authorisation); EU RMP category 3 (required) |
| Countries in which this study is being conducted | Copied | EU PAS Register | Not applicable |
| Is this study being carried out with an established data source? | Copied | EU PAS Register | yes; no |
| Sources of data | Copied | EU PAS Register | Not applicable |
| What is the scope of the study? | Copied | EU PAS Register | Not applicable |
| Primary scope | Copied | EU PAS Register | Not applicable |
| What is the main objective of the study? | Copied | EU PAS Register | Not applicable |
| Full protocol available | Derived | EU PAS Register | Document; not submitted |
| Study Results available | Derived | EU PAS Register | Document; not submitted |
| Other study registration identification numbers and URLs as applicable | Copied | EU PAS Register | Not applicable |
| Study drug information: Brand product name | Copied | EU PAS Register | Not applicable |
| Study drug information: active substance (INN) | Copied | EU PAS Register | Not applicable |
| Study drug information: substance class (ATC) | Copied | EU PAS Register | Not applicable |
| Study design | Copied | Sultana et al dataset1 | Study design |
| Use of reference drug for formal comparison | Copied | Sultana et al dataset1 | Use of reference drug for formal comparison |
| Drug type | Copied | Sultana et al dataset1 | Drug type |
| Marketing authorisation procedure | Derived (taken from PRAC meeting minutes for those studies found there; otherwise, public data from article 57 database was consulted by product name (if available) or active substance – if unclear (e.g. marketing authorisation may have changed over time) – the EMA’s medicine-related data spreadsheet available on the website was used as a complement | PRAC meeting minutes, public data from article 57 database2 and EMA’s medicine-related data spreadsheet3 | Marketing authorisation procedure |
| Availability of study acronym in EU PAS Register | Derived | EU PAS Register (including uploaded documents if available) | yes; no |
| Study acronym | Copied | EU PAS Register (including uploaded documents if available) | Not applicable |
| Availability of protocol number in EU PAS Register | Derived | EU PAS Register (including uploaded documents if available) | yes; no |
| Protocol number | Copied | EU PAS Register (including uploaded documents if available) | Not applicable |
| Availability of EMA regulatory number | Derived | EU PAS Register (including uploaded documents if available) | yes; no |
| EMA regulatory number | Copied (if more than one number was available, all were considered) | EU PAS Register (including uploaded documents if available) | Not applicable |
| PASS Scope: Assess safety concerns | Derived (study objectives mentions focus on assessing any safety concerns) | EU PAS Register (including uploaded documents if available) | yes; no |
| PASS scope: Drug Utilisation | Derived (study objectives mentions focus on drug utilisation, drug use patterns including off-label use) | EU PAS Register (including uploaded documents if available) | yes; no |
| PASS scope: assesses effectiveness of RMM | Derived (study objectives mentions the assessment of the effectiveness of risk minimisation measures e.g., educational materials, pregnancy prevention programme, etc.) | EU PAS Register (including uploaded documents if available) | yes; no |
| PASS scope: Special Population | Derived (if EU PAS Register field “Population under study” mentioned only age and gender consider “no” unless there is an age group <18 years-old or >65-years old, in which case, we considered also the fields “Brief description of the study” and “Main objective(s)” and if those age groups were also specifically mentioned, we considered it was a special population. In addition, if an additional category was mentioned under “other population” (e.g renal impaired), we considered it a special population) | EU PAS Register (including uploaded documents if available) | yes; no |
| PASS found in PRAC meeting minutes | Derived (searching for PASS using any of the available study identifiers) | PRAC meeting minutes | yes; no |
| PRAC meeting minutes: Year and Month the meeting occurred | Copied | PRAC meeting minutes | Not applicable |
| PRAC meeting minutes: minutes' PASS related sub-section in which study is found | Copied | PRAC meeting minutes | Protocol/ Results/ Blank if not classifiable) |
| PRAC meeting minutes: EMA Procedure Number | Copied | PRAC meeting minutes | Not applicable |
| PRAC meeting minutes: Entry related to PASS mentioned study acronym? | Derived | PRAC meeting minutes | yes; no |
| PRAC meeting minutes: Entry related to PASS mentioned protocol number? | Derived | PRAC meeting minutes | yes; no |
| PRAC meeting minutes: Entry related to PASS mentioned study title? | Derived | PRAC meeting minutes | yes; no |
| PRAC meeting minutes: Procedure Scope | Copied | PRAC meeting minutes | Not applicable |
| PRAC meeting minutes: Background information | Copied | PRAC meeting minutes | Not applicable |
| PRAC meeting minutes: PRAC comments | Copied | PRAC meeting minutes | Not applicable |
| PRAC meeting minutes: Is there an entry related with the final study report? | Derived | PRAC meeting minutes | yes; no |
| PASS found in EPAR Procedural Steps? | Derived (searching for PASS using any of the available study identifiers) | EPAR of the concerned medicinal product covered in the PASS– Procedural steps taken and scientific information after authorisation | yes; no; Not applicable (e.g. PASS concerns a NAP) |
| EPAR Procedural Steps: Entry related to PASS mentioned study acronym? | Derived | EPAR – Procedural steps taken and scientific information after authorisation | yes; no |
| EPAR Procedural Steps: Entry related to PASS mentioned protocol number? | Derived | EPAR – Procedural steps taken and scientific information after authorisation | yes; no |
| EPAR Procedural Steps: Entry related to PASS mentioned study title? | Derived | EPAR – Procedural steps taken and scientific information after authorisation | yes; no |
| EPAR Procedural Steps: Application Number | Copied | EPAR – Procedural steps taken and scientific information after authorisation | Not applicable |
| EPAR Procedural Steps: Scope | Copied | EPAR – Procedural steps taken and scientific information after authorisation | Not applicable |
| EPAR Procedural Steps: Variation code(s) | Copied | EPAR – Procedural steps taken and scientific information after authorisation | Not applicable |
| EPAR Procedural Steps: Opinion/Notification issued on; Commission Decision Issued / amended on | Copied (if both available, took the Commission Decision date) | EPAR – Procedural steps taken and scientific information after authorisation | Date |
| EPAR Procedural Steps: Product Information affected | Copied | EPAR – Procedural steps taken and scientific information after authorisation | SmPC; PL; Annex II |
| EPAR Procedural Steps: Summary | Copied | EPAR – Procedural steps taken and scientific information after authorisation | Not applicable |
| PASS results available in other source? (for PASS involving NAP) | Derived | EMA website: “Outcomes for active substances contained in nationally authorised products” (10) and the EMA database of referrals (REF). | yes; no |
| Reg Outcome info available? | Derived | Based on all information retrieved in the abovementioned documents | yes; no |
| Reg Outcomes as provided in the source | Derived | Based on all information retrieved in the abovementioned documents | See predefined regulatory outcome labels selected from source text in Supplementary Table 2 |
| Reg Outcomes as (re-classified) | Derived | Based on “Regulatory Outcomes as provided in the source” | See final regulatory outcome classification in Supplementary Table 2 |
| Ascertainment level | Derived based on criteria described in Methods | Based on all information retrieved in the abovementioned documents | Certain; Possible |
| Reason for “possible” | Derived based on criteria described in Methods | Based on all information retrieved in the abovementioned documents | Not applicable |
| Supporting evidence for Reg Outcome | Derived (documents where regulatory outcome information was found) | EU PAS Register; PRAC Meeting Minutes; EPAR Procedural Steps; Other[specify] | EU PAS Register; PRAC meeting minutes; EPAR Procedural; Other[specify] |

*1 Sultana J, Crisafulli S, Almas M, Antonazzo IC, Baan E, Bartolini C, et al. Overview of the European post‐authorisation study register post‐authorization studies performed in Europe from September 2010 to December 2018. Pharmacoepidemiology and Drug Safety. 2022;31(6):689-705*

*2 European Medicines Agency. Public data from Article 57 database [available from* [*https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/data-medicines-iso-idmp-standards-post-authorisation/public-data-article-57-database*](https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/data-medicines-iso-idmp-standards-post-authorisation/public-data-article-57-database)*]*

*3 European Medicines Agency. Download medicine data [available from* *https://www.ema.europa.eu/en/medicines/download-medicine-data]*

***Supplementary Table 2 - MDS and non-MDS PASS design and drug type***

|  |  |  |  |
| --- | --- | --- | --- |
|  | **MDS** | **Non-MDS** | **Total** |
|  | **n (%)** | **n (%)** | **n (%)** |
|  | **N= 42 (100)** | **N= 42 (100)** | **N= 84 (100)** |
| **Study design** | | | |
| **Cohort study** | 17 (40.5) | 12 (28.6) | 29 (34.5) |
| **Descriptive study** | 13 (31.0) | 16 (38.1) | 29 (34.5) |
| **Cross-sectional study** | 6 (14.3) | 7 (16.7) | 13 (15.5) |
| **Nested case-control study** | 2 (4.8) | 2 (4.8) | 4 (4.8) |
| **More than 1 study design** | 3 (7.1) | 1 (2.4) | 4 (4.8) |
| **Unknown** | 0 (0.0) | 3 (7.1) | 3 (3.6) |
| **Other types of analytic studies** | 0 (0) | 1 (2.4) | 1 (1.2) |
| **Case-control study** | 1 (2.4) | 0 (0.0) | 1 (1.2) |
| **Inclusion of a Comparison Group** | | | |
| **Yes** | 15 (35.7) | 6 (14.3) | 21 (25.0) |
| **No** | 26 (61.9) | 34 (81.0) | 60 (71.4) |
| **Unknown** | 1 (2.4) | 2 (4.8) | 3 (3.6) |
| **Drug type** | | | |
| **Biologic** | 3 (7.1) | 8 (19.0) | 11 (13.1) |
| **Non-biologic** | 35 (83.3) | 32 (76.2) | 67 (79.8) |
| **None** | 1 (2.4) | 1 (2.4) | 2 (2.4) |
| **Unknown** | 3 (7.1) | 1 (2.4) | 4 (4.8) |

**Abbreviations**: MDS = multidatabase PASS; RMM = risk minimisation measure.

Variables’ categories were taken from the dataset of Sultana et al (9). See Supplementary Material Table 1.

***Supplementary Table 3- Description of studies by PASS RMP category***

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Imposed1** | **Non-imposed** | **Total** |
|  | **n (%)** | **n (%)** | **n (%)** |
|  | **N= 23** | **N= 61** | **N= 84** |
| **MDS/Non-MDS** | | | |
| **MDS** | 12 (52.2) | 30 (49.2) | 42 (50.0) |
| **Non-MDS** | 11 (47.8) | 31 (50.8) | 42 (50.0) |
| **PASS scope** | | | |
| **Drug utilisation** | 16 (69.6) | 33 (54.1) | 49 (58.3) |
| **Assess safety concerns** | 11 (47.8) | 29 (47.5) | 40 (47.6) |
| **Assess effectiveness of RMM** | 11 (47.8) | 15 (24.6) | 26 (31.0) |
| **Special Population** | | | |
| **Yes (**e.g renal impaired, hepatic impaired, immunocompromised, pregnant women, paediatric, elderly)2 | 7 (30.4) | 30 (49.2) | 37 (44.0) |
| **Study design** | | | |
| **Cohort study** | 8 (34.8) | 21 (34.4) | 29 (34.5) |
| **Descriptive study** | 8 (34.8) | 21 (34.4) | 29 (34.5) |
| **Cross-sectional study** | 6 (26.1) | 7 (11.5) | 13 (15.5) |
| **Nested case-control study** | 0 (0.0) | 4 (6.6) | 4 (4.8) |
| **More than 1 study design** | 1 (4.3) | 3 (4.9) | 4 (4.8) |
| **Unknown** | 0 (0.0) | 3 (4.9) | 3 (3.6) |
| **Other types of analytic studies** | 0 (0) | 1 (1.6) | 1 (1.2) |
| **Case-control study** | 0 (0) | 1 (1.6) | 1 (1.2) |
| **Comparative** | | | |
| **Yes** | 4 (17.4) | 17 (27.9) | 21 (25.0) |
| **No** | 18 (78.3) | 42 (68.9) | 60 (71.4) |
| **Unknown** | 1 (4.3) | 2 (3.3) | 3 (3.6) |
| **Drug type** | | | |
| **Biologic** | 0 (0) | 11 (18.0) | 11 (13.1) |
| **Non-biologic** | 20 (87) | 47 (77.1) | 67 (79.8) |
| **None** | 0 (0) | 2 (3.3) | 2 (2.4) |
| **Unknown** | 3 (13.0) | 1 (1.6) | 4 (4.8) |
| **Marketing authorisation procedure3** | | | |
| **CAP** | 7 (30.4) | 46 (75.4) | 53 (63.1) |
| **NAP** | 16 (69.6) | 14 (23.0) | 30 (35.7) |
| **Mixed4** | 0 (0.0) | 1 (1.6) | 1 (1.2) |

**Abbreviations**: CAP = centrally authorised product; MDS = multidatabase PASS; NAP = nationally authorised product; RMM = risk minimisation measure; RMP = Risk Management Plan.

Variables’ categories were taken from the dataset of Sultana et al (9). See Supplementary Material Table 1.

1 There was only one PASS of RMP category 2

**2** Based on EU PAS Register field “Population under study” when there was mention to “other population (e.g renal impaired, hepatic impaired, immunocompromised, pregnant women) or when there was reference to age <18 years-old and >65 years-old if the study description and objective fields in EU PAS Register suggest these age groups were of special interest.

3 Referent to the original authorisation procedure by which the drug was approved and not necessarily that the PASS was being conducted to support the original marketing authorisation procedure.

4 Included an active substance for which some brands were approved though central and others through national authorisation procedures.

***Supplementary Table 4 - PASS traceability across sources and extent of information available (by imposed/non-imposed PASS)***

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Imposed (RMP Category 1 and 2)a** | | | **Non-imposed (RMP Category 3)** | | | **Total** | | |
|  | CAP (N=7) | NAP  (N=16) | Overall  (N=23) | CAPb  (N=47) | NAP  (N=14) | Overall  (N=61) | CAPb  (N=54) | NAP  (N=30) | Overall  (N=84) |
| **Availability of PASS within PRAC minutes, n(%)** | 7 (100.0) | 12 (75.0) | 19 (82.6) | 38 (80.9) | 2 (14.3) | 40(65.6) | 45 (83.3) | 14 (46.7) | 59 (70.2) |
| **PRAC comments available, n(%)** | 3 (42.9) | 11 (68.8) | 14 (60.9) | 2 (4.3) | 0 (0.0) | 2 (3.3) | 5 (9.3) | 11 (36.7) | 16 (19.0) |
| **Availability of PASS in Procedural Steps Document (CAP), n(%)** | 7 (100) | NA | 7 (30.4) | 38 (80.9) | NA | 38 (62.3) | 45 (83.3) | NA | 45 (53.6) |
| **Summaryc available, n(%)** | 6 (85.7) | NA | 6 (26.1) | 11 (23.4) | NA | 11 (18.0) | 17 (31.5) | NA | 17 (20.2) |
| **Availability in outcomes of NAPs/referral webpages (NAP), n(%)** | NA | 11 (68.8) | 11 (47.8) | NA | 2 (14.3) | 2 (3.3) | NA | 13 (43.3) | 13 (15.5) |

**Abbreviations**: CAP = Central Authorised Procedure; NA = Not applicable; NAP = National Authorised Procedure; PASS = Post Authorisation Safety Study; PRAC = Pharmacovigilance Risk Assessment Committee; RMP = Risk Management Plan.

a There was only one PASS of RMP category 2

b Includes an active substance that had some brands approved though central and others through national authorisation procedures

c Summary of the European Public Assessment Report Procedural Steps taken and scientific information after authorisation

***Supplementary Table 5 – Availability of regulatory outcome information (by imposed/non-imposed PASS)***

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Imposed (RMP Category 1 and 2)a** | **Non-imposed (RMP Category 3)** | **Total** |
|  | **N=23** | **N=61** | **N=84** |
| **Overall regulatory Outcome information available1, n(%)** | **18 (78.3)** | **21 (34.4)** | **39 (46.4)** |
| **Certain, n(% on those available)** | 7 (38.9) | 16 (76.2) | 23 (59.0) |
| **Possible, n(% on those available)** | 11 (61.1) | 5 (23.8) | 16 (41.0) |

**Abbreviations**: RMP = Risk Management Plan

1 Any text related to a regulatory outcome was considered. The level of confidence of an investigator in classifying the regulatory outcome(s) for a specific study was also scored as “certain”, whenever the available information clearly indicate that the regulatory outcome was a consequence of the concerned PASS, or “possible”: whenever it was not clear what was the regulatory outcome and/or it resulted from the PASS of interest or other procedures (e.g., both PASS reports and Periodic Safety Update Reports (PSURs) were submitted).

a There was only one PASS of RMP category 2

***List of supplementary figures and legends***

***Supplementary Figure 1 - Availability of regulatory outcome by year of study conclusion (stratified by Authorisation Procedure)***

Abbreviations: CAP = Central Authorised Procedure; NAP = National Authorised Procedure

***Supplementary Figure 2 – Availability of regulatory outcome and types following submission of PASS report as mentioned in the source (categories are not mutually exclusive) among all included PASS including if they were missed either because the study was not traceable or the information was not evaluable***

Abbreviations:MDS = Multidatabase PASSs, RMM = Risk minimisation measure, SmPC = Summary of Product Characteristics, PL = Product Leaflet, PV = Pharmacovigilance.