



RESEARCH ARTICLE

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Teratogenicity: analysis of European risk management plan summaries.

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ARTICLE INFO ABSTRACT



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Keywords:

Safety concerns, additional risk minimisation measures, Summary of product characteristics, Important identified risk, Important potential risk, Missing information

Background: A judicious decision is significant in clinical practice when a known teratogenic medicine is prescribed for women considering her ailment or avoiding its exposure due to foetal harm. For this careful balance, European medicine agency (EMA) and marketing authorization holder provides complete pharmacological information regarding each medicinal product for clinicians to take informed decision. Proactively, EMA publishes the safety concerns included in the risk management plan (RMP) and subsequent risk minimisation measures.

Objectives: The objective of present study is to review safety information published in RMP summaries for teratogenic medicines and to explore the proactive approaches considered to improve its benefit-risk balance.

Method: All safety concerns (SC) included in the RMPs of originator centrally authorised products (CAPs), authorised between 1 August 2012 and 31 December 2022, were collected from the European Public Assessment Report. Teratogenicity SCs were categorized by Anatomical Therapeutic Classification code, year of authorisation, category of safety concern and type of risk minimisation measures. Further, Summary of Product Characteristics (SmPC) were reviewed for safety information.

Results: During the study period, 324 CAPs were found to be associated with teratogenicity SC. Antineoplastic and immunomodulating agents had teratogenicity SCs most often. Out of 324 CAPs, 221 product SCs were categorized as missing information. Twenty-nine products had additional risk minimisation measures (aRMMs) which addressed teratogenicity SC. These aRMMs consisted of educational program, controlled distribution system and pregnancy prevention program targeted towards healthcare professionals and/or patients. Further, 155 additional pharmacovigilance activities were identified in these product RMP summaries for teratogenicity risk. Content analysis of SmPC revealed that important information on the use of medicines during pregnancy is missing.

Conclusion: More than half of the RMP summaries described teratogenicity as SC for the medicines approved during the study period. Post-authorization data on teratogenic medication should be actively collected and ensured to reach the clinicians via SmPC and/or aRMMs to keep them updated and enhance evidence-based decision making.

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Introduction

Drug utilisation studies suggests that majority of pregnant women use at least one medication to treat acute or

chronic disorders. Medication may be taken by women for an ongoing treatment before pregnancy or initiated a medication during pregnancy for pregnancy specific conditions or for any conditions which may be worsened



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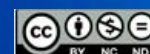
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due to pregnancy. It is observed that approximately 80% of women use prescribed or OTC medication during pregnancy (Lupattelli et al., 2014; Trønnes et al., 2017; European Medicines Agency, 2023).

Any adverse effect of a teratogenic medicine on the foetus via mother will not be immediately evident, but it may result into a lifelong detrimental effect. If a medicine used by mother for a therapeutic effect is teratogenic in nature, it significantly impacts its benefit-risk balance. To improve the benefit-risk balance, appropriate interventions are necessary to minimize the risks to mother and foetus. As alternative therapy is not available in many instances, using potential teratogenic medications in women of childbearing age needs to be warranted (Genetic Alliance & District of Columbia Department of Health, 2010; Schwarz et al., 2005; Honein et al., 2004). In Europe, very few medicines are licensed explicitly for use in pregnancy (European Medicines Agency, 2023). There are few clinical trials being conducted during pregnancy and so, limited information is available at the time of marketing authorisation application. Therefore, benefit-risk balance of a medicine is monitored continuously in post-marketing phase which is stated in the strategic plans of European Medicines Agency (EMA) as proactive pharmacovigilance (EMA 2023). New legislation for pharmacovigilance was applied in the European Union (EU) in July 2012 and to support its implementation, Guideline on good pharmacovigilance practices (GVP) were adopted. This led to restricted use of teratogenic medicines by means of various risk minimisation programs (Mayall et al., 2014).

The EU-RMP is a dynamic document being updated throughout the lifecycle of the medicinal product. A discussion on the exposure in pregnant women is a mandatory part of the EU RMP and, if appropriate, teratogenicity risk can be included as an important safety concern in the RMP. In addition, pharmacovigilance activities and aRMMs are proposed to avoid embryo-foetal exposure. EMA published GVP Module V risk management systems (Rev 2) in 2017 making it more proactive by further clarifying the activities, a RMP should focus on (EMA GVP, 2023). The objective of the present study is to identify teratogenicity safety concerns along with the risk minimization measures and pharmacovigilance activities published in RMP summaries and to explore the specific safety information laid down in SmPC for this patient group which guides clinicians in decision making.

Method

A content analysis of RMP summaries and risk minimisation measures was conducted for teratogenic medicine approved by the EMA via centrally authorised procedure between August 2012 and December 2022.

Publication of RMP summary on EMA website was made mandatory along with the release of GVP Module V in 2012 to increase transparency and public access to relevant information on medicines, therefore study period of past ten years was considered. Given that, Generics and biosimilars are expected to follow the originator product for RMP strategy, these were excluded from the study. Finally, products with no RMP summary published were not further analysed. Figure 1 shows the selection process.

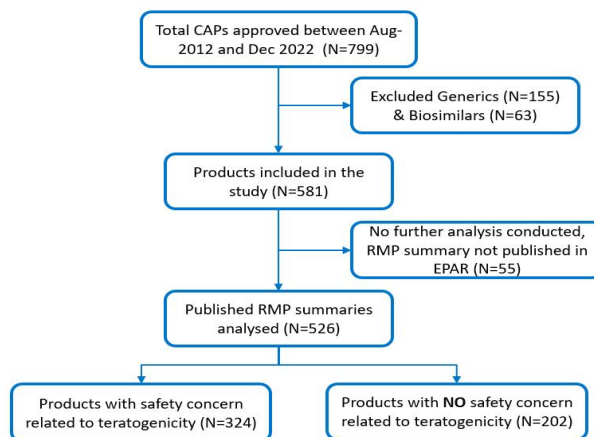


Figure 1: Flow diagram of 2012-2022 RMP summary selection for content analysis. (CAP: Centrally Authorised Products; EPAR: European Public Assessment Report)

Data source and collection

EMA publishes European Public assessment report (EPAR) (including RMP summary) once the medicinal product has a positive decision from the European Commission. A list of EPARs for human medicines was downloaded from EMA's Website. This list provides the information on authorized medicines. Data identified from this list was: Medicine Name, active substance name, therapeutic area, indication, date of authorization, Anatomical Therapeutic Classification (ATC) code and EPAR URL. RMP summary and ATC group for each product were obtained from EPARs and WHO Collaborating Centre for Drug Statistics ((WHOCC - ATC/DDD Index) respectively).

Data extracted from analysis of RMP summaries were

- safety concerns (SC) related to use during pregnancy or effect on pregnancy outcome or effect on foetus (hereafter, all these safety concerns will be referred as Teratogenicity SC),
- category of SC (important identified risk or important potential risk or missing information),

- proactive approaches to minimize the teratogenic risk (SmPC and additional risk minimisation measures) and
- approaches to investigate the SC or to assess the effectiveness of aRMM (additional pharmacovigilance activity).

Further, Annex I (Summary of Product Characteristics) of EPAR's product information were explored for safety communication messages delivered to target population.

Data Analysis

Descriptive statistics were used to present the data extracted from RMP summaries. All analysis were performed in Microsoft Excel 365.

Results

Identification of Teratogenicity SCs from RMP summaries

A total of 581 RMP summaries (or products) met evaluation eligibility criteria. There was no teratogenicity SC identified in 35% (N=202) of published RMP summaries. Remaining 324 centrally authorized products (CAPs) were associated with Teratogenicity SC which represents approximately 41% (324/799) of all products authorized in study period. Among these 324 SCs, 4% (n=14) were categorized in the RMP as important identified risks (IIR), 28% (n=89) were categorized as important potential risks (IPR) and 68% (n=221) were categorized as missing information (MI). The proportion of CAPs approved with a Teratogenicity SC showed variations between 2012 and 2022, ranging from 37% in 2017 to 77% in 2021 (see Fig. 2).

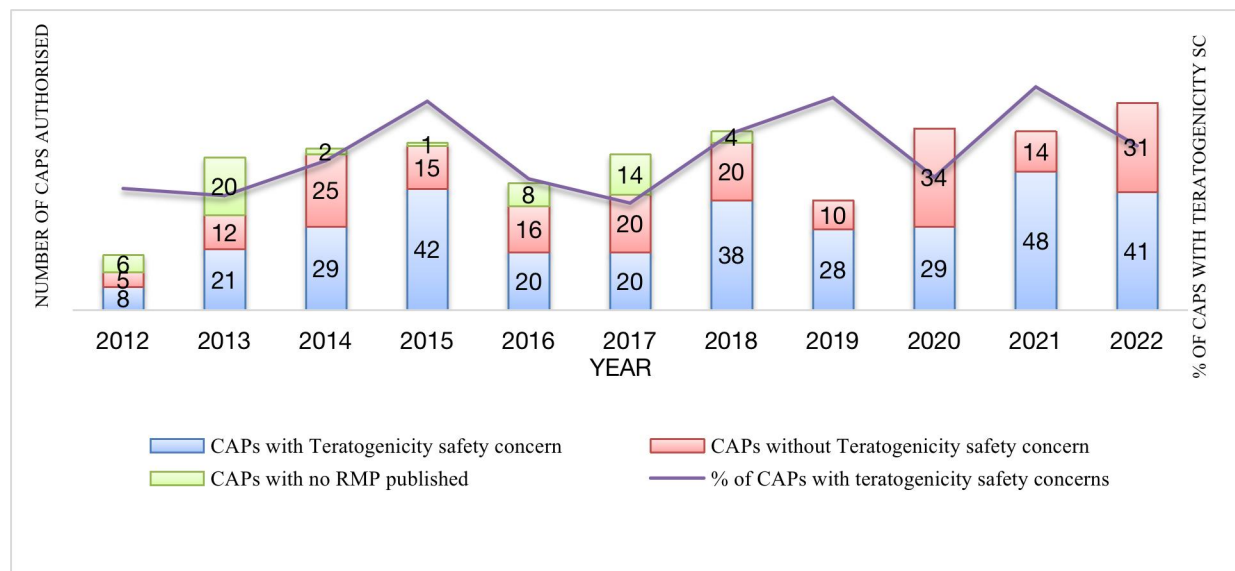


Figure 2: Number of CAPs approved yearly with and without Teratogenicity safety concerns (CAP: Centrally authorised products; RMP: Risk management plan; SC, Safety concern)

Identification of therapeutic group of Medicinal Products:

Antineoplastic and immunomodulating agents had teratogenicity SCs most often (n=101), followed by Anti-infectives for systemic use (n=54) and Alimentary tract and metabolism (n=41). When compared to the overall number of CAPs authorized in each ATC group,

dermatologicals most frequently had teratogenicity safety concerns, as 75% of products authorized in this ATC group had at least one safety concern (Table 1) and all Antiparasitic products, insecticides and repellent had teratogenicity safety concerns (100%). Other ATC groups with a high rate of products with teratogenicity safety concerns are mentioned in table 1.

Table 1: Centrally authorized products (CAPs) with and without teratogenicity as safety concerns per Anatomical Therapeutic Chemical Classification System (ATC) group

ATC group	CAPs with Teratogenicity safety concerns (n=324)	CAPs without Teratogenicity safety concerns (n=202)	% Of CAPs with Teratogenicity safety concerns
A - Alimentary tract and metabolism	41	18	69%
B - Blood and blood forming organs	26	12	68%
C - Cardiovascular system	16	6	73%
D - Dermatologicals	6	2	75%
G - Genito urinary system and sex hormone	2	3	40%
H - systemic hormonal preparations, excluding sex hormones and insulins	3	11	21%
J - Anti-infectives for systemic use	54	32	63%
L - Antineoplastic and immunomodulating agents	101	64	61%
M - Musculo-skeletal system	5	4	56%
N - nervous system	35	13	73%
P - Antiparasitic products, insecticides, and repellent	1	0	100%
R- Respiratory system	14	20	41%
S - sensory organs	7	6	54%
V - Various	9	11	45%
Not yet assigned	4	0	100%
Total	324	202	62%

CAP, centrally authorized product; ATC, Anatomical Therapeutic Chemical Classification System

Analysis of Proactive approaches for Risk Minimisation of teratogenicity SC**Safety data specified in SmPCs:**

The SmPC sections most frequently used to address teratogenicity SC were sections 4.3 (Contraindications),

4.4 (special warnings and precautions for use), 4.6 (Fertility, Pregnancy and Lactation) and 5.3 (Preclinical safety data). Distribution of all types of safety concerns in SmPC is provided in Table 2.

Table 2: Summary of Product Characteristics (SmPC) sections listed as routine risk minimisation measures for teratogenicity risk.

SmPC Section ^a	4.2	4.3	4.4	4.5	4.6	4.8	5.1	5.2	5.3
Important identified risk	1	8	7	1	14	1	0	1	7
Important Potential risk	4	19	36	6	89	2	0	0	80
Missing information	3	7	30	1	221	1	3	3	186
Total	8	34	73	8	324	4	3	4	273

^a SmPC sections never used are not included in the table. Values are distributed from high (dark red) to low (green). Dark red if the SmPC section has been used >20 times to warn for the use during pregnancy. Green if the SmPC section was never used to warn for the use during pregnancy.

SmPC, Summary of Product Characteristics

Individual SmPCs were further analysed on safety information for HCPs and pregnant women. Of 324 products, 11 % (n=34) are contraindicated in pregnancy (8 IIR, 19 IPR, 7 MI), 66 % (n=214) were not recommended during pregnancy (1 IIR, 66 IPR, 147 MI), 21 % SmPCs (n=69) allowed the use in pregnant women (4 IIR, 3 IPR, 62 MI), among which three SmPCs allow the usage only if no alternative is available and 1 % (n=3) SmPCs did not provide any recommendation for use during pregnancy (1 IPR, 2 MI). Remaining four products were found to not indicated in pregnancy or not intended for use in adults i.e., two oral contraceptives which are not indicated in Pregnancy are categorized as MI in RMP summary and two products which are not intended for use in adults were categorized as IIR and MI.

It was observed that only 12 % (n=39) of SmPCs clearly informed that medicine was able to cross the placental barrier, 5 % (n=15) of SmPCs mentioned that it was unknown whether the medicine crossed the placenta in humans and in remaining 83 % (n=270) of SmPCs, no information was available whether the drug crossed (or not) the placental barrier.

A total of 89 % SmPCs (n=290) reported the existence of pre-clinical studies that assessed the teratogenic effect or reproductive toxicity of the medicine in animals. Remaining, 10 % (n=33) SmPCs reported that no animal studies had been conducted and one SmPC was found to

have nothing mentioned related to pre-clinical studies. Of the 290 SmPCs reporting the existence of pre-clinical studies, 89.3 % (n=259) described the results of the animal studies in SmPC section 5.3. In contrary, 99 % (n=322) of SmPCs reported to have limited or no clinical information available from the use of medicine in pregnant women and two SmPCs clearly mentioned that no clinical studies had been carried out in pregnant women.

Clinical experience data (from epidemiological studies or registries) was identified in 8 % (n=26) of SmPCs only (including three SmPCs which provided clinical experience data of same therapeutic class).

In 46 % (n=148) of SmPCs a recommendation for women of child-bearing potential to use contraceptive measures was stated along with other recommendations on contraception and to avoid pregnancy when using the product. SmPCs did not provide any information on how to manage the exposure of the medicine to pregnant women.

Analysis of Additional risk minimization measures

During the study period, 9 % (n=29) products had aRMMs which addressed teratogenicity SC. The proportion of teratogenicity SCs for which aRMMs were implemented was variable over calendar time, ranging from no aRMMs in 2016 to 29 % in 2013 (Fig 3).



Figure 3: Teratogenicity SCs with and without aRMMs per marketing authorisation year (SC: Safety concern; aRMMs, additional risk minimisation measure)

The aRMMs implemented for 29 products were educational program (EP), Pregnancy prevention program (PPP) and Controlled distribution system. EP was observed to be implemented for 23 products which are associated with Teratogenicity SC categorized as important identified risks for two products, IPR for 17 products and MI for four. These EPs utilised 51 educational materials as source of communication targeted to HCPs (n=23) and patients (n=28). One of the patient materials is also provided in digital format (audio version). Among these EPs, 57 % (n=13) were implemented for anti-neoplastic and immunomodulating agents and 13 % (n=3) were aimed at the treatment of cardiovascular system (Figure 4).

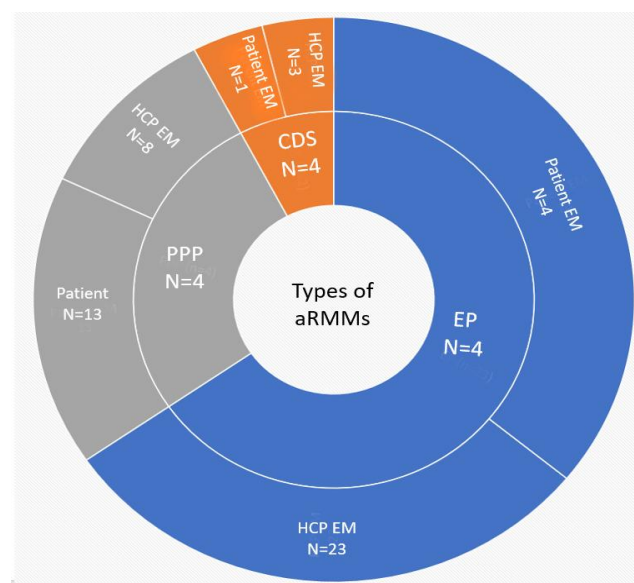


Figure 4: Number and types of additional risk minimisation measures (aRMM). (EP: Educational programme; PPP: Pregnancy prevention programme; CDS: controlled distribution system; HCP: Healthcare professional; EM: Educational material.)

Four products have PPP implemented to address three IIRs and one IPR, all for antineoplastic and immunomodulating agents. All these PPP, had educational tools for HCPs and Patients, Prescribing and dispensing restrictions and counselling for women. Twenty-one EMs were identified as part of 4 PPPs. Thalidomide PPP was found to have highest number of EMs, one material targeted for HCP and 7 for patients. Additionally, Annex IID mentioned the distribution of Pregnancy initial and outcome reporting forms, Adverse reaction reporting forms and post-marketing and compliance assessment. Two products have controlled distribution system implemented to address one IIR and MI each with four EMs.

Analysis of Additional PV activity

It was identified that 155 Additional Pharmacovigilance activity (APA) are ongoing/planned for 132 products with Teratogenicity safety concern (3 IIR, 28 IPR, 124 MI). Ten studies to analyse the effectiveness of aRMMs were listed in the RMP summaries including two Drug Utilization Study to Evaluate the Effectiveness of RMMs. For the remaining 19 products with aRMM, no effectiveness studies were described in RMP summary.

Registry studies were listed most frequently to analyse the safety concern for teratogenicity (n=58). These registries include Pregnancy registries (n=56), one Product registry and one Disease registry with secondary objective to study the exposure in pregnancy. Other studies were described in the EPAR as follows: DUS (n=4), Embryo-Foetal development toxicity study (n=1), Long term safety study (n=9), PASS to investigate a safety concern or pregnancy outcome and PMS (n=69), pharmacokinetics and safety study (n=2) and pregnancy healthcare database study (n=2).

Discussion

More than half of the RMP summaries described teratogenicity as SC for the medicines authorised during the study period. It is evident that EMA is transparent in communicating about product's safety profile in pregnant women along with the safety topic characterization and mitigation. In recent years, several approaches have been taken by the EMA to strengthen the minimisation measure for teratogenic medicine use. e.g., EU-funded research as part of the Pharmacoeconomic Research on Outcomes of Therapeutics by a European Consortium (PROTECT) Consortium, (Dreyer et al., 2015; EMA 2023) workshop on safe use of medicines during pregnancy and breastfeeding, (European Medicines Agency, 2023) Public hearing to assess teratogenic risk of valproate (European Medicines Agency, 2017) and upcoming GVP Guidelines for pregnant and breastfeeding women.

Another finding is that majority of these safety concerns (68 %) were categorized as missing information in the EU-RMP. Because of the ethical, medicolegal, and foetal safety concerns, few pharmacokinetic, pharmacodynamic or clinical trials are conducted during pregnancy and so, safety information in this population is limited. This shows that majority of products authorised are expected to be used in pregnant women and there is a suspicion of different safety profile though information is limited and so it has a place in EURMP as safety concern in accordance with GVP module V.

Further, a large proportion of these safety concerns were described in the EPAR as use in pregnancy (or effect on pregnant women or foetus) without indicating the exact type of effect on women or foetus. Moreover, very few

safety concerns specified the clinical consequence of the exposure during pregnancy. However, it is preferable to include the undesirable clinical outcomes as a consequence of the exposure during pregnancy in the EPAR. For example, Xospata RMP summary (Embryo-foetal lethality, suppressed foetal growth, and teratogenicity) specifies what the risk is and provides evidence from preclinical studies as rationale for risk categorization. This is also emphasized in the current GVP Module V revision 2.

One of the significant routine risk communication tools is SmPC which is the major source of information for healthcare professionals (HCPs). Study showed that SmPC guidelines were followed by presenting safety information related to pregnancy in section (4.6 'Fertility, Pregnancy and Lactation') (European Commission, 2009) and other SmPC sections being cross referred to provide warnings and to advise on contraceptive measures or to avoid medicine or pregnancy. Further, SmPC content analysis revealed that important information was missing on the use of medicines in pregnancy. Of the 324 SmPCs analysed, around 83 % did not mention whether the drug crossed the placental barrier, almost 92 % stated that there was no clinical experience on the use of medicine during pregnancy.

SmPC is provided to HCPs by MAH in agreement with regulatory agencies for consultation. Therefore, it is essential that it provides complete information for decision making. However, this knowledge gap is a critical question from last few years (Trønnes et al., 2017; Arguello et al., 2007). In the present study it was observed that completeness of information in SmPC was missing. e.g., around 83% of SmPCs does not mention whether the drug crossed the placental barrier and 54 % lack information about the medicine use in women of child-bearing potential.

Non-clinical developmental and reproductive toxicity (DART) testing supports in extrapolating its results in humans. These tests are applied in predicting human risks; therefore, it is significantly emphasized by EMA to support human clinical trials and marketing authorization for pharmaceuticals (European medicines Agency, 2008; European medicines Agency, 2023). However, study observed that 10 % of SmPCs declared that no animal studies had been conducted.

Knowledge gap in pregnant women is because this population is being excluded from clinical studies. It was supported by this study, 99 % of SmPCs mentioned limited data from clinical studies. However, regulatory agencies at global level are taking steps to shift their focus from exclusion to inclusion of pregnant women in clinical studies. EMA too is participating in such activities by assisting a consortium (ConcePTION project) (ConcePTION consortium, 2023) and developing GVP

Guideline: Pregnant and Breastfeeding Women (European medicines Agency, 2023).

About 68 % of safety concerns are categorized as missing information, reflecting the knowledge gap as this population is being excluded in the pre-authorisation phase. Anticipation is to get more post-marketing data which allows for further reclassification of SCs. Therefore, in absence of pre-marketing study data, clinical experience is vital for clinicians when deciding to initiate or stop a given therapy. However, only 8 % of SmPCs provided some information regarding the existence of clinical experience in pregnant women. Though several APAs are implemented to collect data on SC for products authorized since 2012, little or no information from registries or other studies are present in SmPC.

Analysis of aRMMs observed that PPP and Controlled distribution system were implemented mainly for IIRs and EPs for IPRs. This suggests that the strong causal association between product and teratogenicity risk is a determining factor for the necessity of an PPP or CDS which includes various elements aiming to minimise exposure during pregnancy. It also reflects that educational material is the major tool for safety communication wherein there is suspicion of a risk.

In all the aRMMs, means of communication to HCPs or patients is EM. It often is directed towards HCPs and patients with further instructions on use of effective contraception, patient informing Doctor on becoming pregnant and to know the harm on baby. EM is largely being considered as aRMM as it is comprehensive and useful tool to create awareness and easy to produce, though implementation being challenging in different regions of Europe (Hapani et al., 2022).

More than half of the missing information had APA in place to retrieve more information on teratogenicity or pregnancy outcomes. This is in accordance with GVP Module V. Further, Study to Evaluate the Effectiveness of RMMs were not discussed in RMP summaries for 19 products with aRMMs. These studies are important to decide whether RMMs are adequate or requires amendment or if any corrective actions are required.

Additional risk minimisation measures were required for almost 43 % of these safety concerns categorised as IIRs. Seven products are not contraindicated but SmPC mentions that it is not recommended in pregnancy and there is no aRMMs for it. So, it is the physician's discretion to take a decision based on whether the intended benefits of the product outweigh the risks This clearly depicts that there is wide knowledge gap and so more studies are required to acquire more information and strong methods to distribute the information for appropriate decision in pregnant women.

Study Limitations

As the data was collected from summarized documents available on EMA website (RMP summaries and other EPAR documents), few information like packaging and labelling used to minimise the risk is not included in the study. Further, 9 % of products did not have RMP summary published, and so results lack the information for these products. In the study, nonclinical data was assessed from the SmPC. However, nonclinical data is not presented in RMP summary which being the limitation though it is discussed in EURMP. Availability of complete EURMP may improve data analysis.

Conclusion

The present study confirms that pregnant women being an ignored population in clinical studies, have a place in EURMP to categorize and characterize the safety profile of medicine and to manage the risk appropriately. Revision of regulatory guidelines suggest awareness at the level of the EMA and Marketing authorization holder to improve the risk benefit balance of a product. Such initiative by regulators will enhance the evidence-based decision making by allowing the active collection of data from studies and updates to sources of information.

Conflict of Interest

Author is not affiliated with or involved in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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