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Human Medicines Division

Research projects conducted under the remit of the PRAC Impact Strategy

Overview of impact studies

EMA has contracted several institutions to conduct research projects collecting and analysing real-world data from clinical practice to help monitor the safety and effectiveness of human medicines. Alternatively, research may be conducted collaboratively by national competent authorities as members of the European Medicines Regulatory Network (EMRN).

The following table includes information on **completed** impact studies launched under the remit of the PRAC Impact Strategy, including information on the research framework, safety concern(s), risk minimisation measures (RMM), regulatory procedure for RMM implementation, study objectives, and publication of the results.

Further information is available from the HMA-EMA Catalogue of Real-World Data Studies.

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Impact studies conducted under the remit of the PRAC Impact Strategy

	Study title (*short title*) EU PAS number^ Framework[$]	**Safety concern and RMM** Regulatory procedure	**Study objectives**	**Status** Publication of results
1	**A European multicentre drug utilisation study of the impact of regulatory measures on prescribing of codeine for pain in children** (*Codeine DUS*) EUPAS17093 Framework: EMRN	**Respiratory depression:** • Restriction in use to children aged ≥12 years at lowest effective dose and shortest time period where pain cannot be relieved with ibuprofen or paracetamol • Contraindication in children undergoing tonsillectomy or adenoidectomy for obstructive sleep apnoea and in CYP2D6 ultra-rapid metabolisers • Public health communication Regulatory procedure: EMEA/H/A-31/1342*	1. To measure the impact of RMMs for codeine for the treatment of pain in children by measuring trends in prescribing over the period Q1/2010 and the end of Q4/2014 (or Q2/2015) to identify any temporal associations with the 2013 referral and its outcomes. 2. To assess to what extent the data collected can be used for comparisons between countries.	**Completed** Hedenmalm, K, Blake, K, Donegan, K, et al. A European multicentre drug utilisation study of the impact of regulatory measures on prescribing of codeine for pain in children. Pharmacoepidemiol Drug Saf. 2019; 28: 1086–1096. https://doi.org/10.1002/pds.4836
2	**Prescribing patterns of codeine and alternative medicines in children in Europe** (*Alternatives to codeine DUS*) EUPAS32021 Framework: EMRN	**Respiratory depression:** • See study #1 for pain indication; • Contraindication in children aged <12 years for treatment of cough and cold • Not recommended in children aged 12 - 18 years with compromised respiratory function and/or considered CYP2D6 ultra-rapid metabolisers for treatment of cough and cold Regulatory procedures: EMEA/H/A-31/1342 EMEA/H/A-31/1394	1. To assess if the codeine referrals for the treatment of pain and cough or cold in patients below 18 years of age were temporally associated with statistically significant changes in prescribing of alternative analgesics, antitussive agents or cold medicines in this patient population. 2. To describe prescribing trends for codeine and alternative analgesics and antitussives over time in patients below 18 years of age per time period 2.1. in relation to all children in the database during the same time period, 2.2. Stratified by age group (0-11 years and 12-17 years) and by gender.	**Completed** Plueschke, K., Flynn, R., Hedenmalm, K. et al. Prescribing Patterns of Codeine and Alternative Medicines in Children in Europe. Drug Saf 45, 1069–1081 (2022). https://doi.org/10.1007/s40264-022-01214-y
3	**Impact of EU label changes for systemic**	**Cardiovascular risks:**	1. To determine prescription patterns of diclofenac containing products starting at least three years	**Completed**

	diclofenac products: post-referral prescribing trends (*Diclofenac DUS*) EUPAS24089 Framework contract: EMA/2015/26/PH	• NSAIDs should be used at the lowest dose for the shortest duration possible • Contraindication in patients with congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease • Warning that patients with cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should use diclofenac only after careful consideration • Direct healthcare professional communication (DHPC) Regulatory procedure: EMEA/H/A-31/1344*	before the regulatory intervention, stratified by indication, age and gender, and including 1.1 diclofenac initiation rates, 1.2 diclofenac prescribing rates by patients, 1.3 diclofenac prescribing rates by prescriptions, 1.4 diclofenac discontinuation rates, 1.5 dose of diclofenac, 1.6 duration of diclofenac therapy. 2. To determine prescribers' compliance with cardiovascular contraindications and warnings for patients with cardiovascular risk factors in sections 4.3 and 4.4 of the SmPC based on prescription patterns, stratified by indication, age and gender. 3. To determine prescription patterns of alternative medicines (including other systemic NSAIDs, topical NSAIDs, paracetamol, opioids and other chronic pain medication) prescribed in patients where diclofenac has previously been prescribed.	Morales, DR, Morant, SV, MacDonald, TM, et al. Impact of EU regulatory label changes for diclofenac in people with cardiovascular disease in four countries: Interrupted time series regression analysis. Br J Clin Pharmacol. 2021; 87: 1129–1140. https://doi.org/10.1111/bcp.14478 Morales, DR, Morant, SV, MacDonald, TM, et al. Impact of EMA regulatory label changes on systemic diclofenac initiation, discontinuation, and switching to other pain medicines in Scotland, England, Denmark, and The Netherlands. Pharmacoepidemiol Drug Saf. 2020; 29: 296–305. https://doi.org/10.1002/pds.4955
4	**Impact of EU label changes for hydroxyzine products: post-referral prescribing trends** (*Hydroxyzine DUS*) EUPAS26363 Framework contract: EMA/2015/26/PH	**QT-prolongation and cardiac arrhythmia:** • Dose restriction to maximum daily dose of 100 mg in adults, with corresponding changes in the paediatric and elderly populations, and treatment duration as short as possible; • Contraindication in patients with QT interval prolongation, known risk factors to	1. To determine prescription patterns of hydroxyzine containing medicinal products before and after the regulatory intervention, stratified by indication, age and gender, and including 1.1 hydroxyzine initiation rates, 1.2 hydroxyzine prescribing rates by patients,	**Completed** Morales, DR, Macfarlane, T, MacDonald, TM, et al. Impact of EMA regulatory label changes on hydroxyzine initiation, discontinuation and switching to other medicines in Denmark,

		QT interval prolongation i.e., cardiovascular disease, electrolytes imbalance (hypokalaemia, hypomagnesemia), family history of sudden cardiac death, significant bradycardia, concomitant use with other drugs known to prolong the QT interval and/or induce Torsade de Pointes; • Warning against use in the elderly due to the anticholinergic effects; • DHPC; Regulatory procedure: EMEA/H/A-31/1400*	1.3 hydroxyzine prescribing rates by prescriptions, 1.4 hydroxyzine discontinuation rates, 1.5 dose of hydroxyzine, 1.6 duration of hydroxyzine therapy. 2. To determine prescribers' compliance with dose restrictions, contraindications in patients with QT prolongation and risk factors for QT prolongation, and warnings against use in the elderly in sections 4.2, 4.3 and 4.4 of the SmPC based on prescription patterns among patients with a history of the following contraindications, and stratified by indication, age and gender: 2.1 Established cardiovascular disease 2.2 Patients with a recent history of significant electrolytes imbalance (hypokalaemia, hypomagnesaemia) 2.3 Family history of sudden cardiac death 2.4 Recent symptomatic bradycardia (recent code for bradycardia or pulse rate <60 BPM) 2.5 Concomitant use with drugs known to prolong the QT interval and/or induce Torsade de Pointes 3. To determine prescription patterns of alternative medicines prescribed in patients where hydroxyzine has previously been prescribed for anxiety disorders, skin conditions and sleep disorders.	Scotland, England and the Netherlands: An interrupted time series regression analysis. Pharmacoepidemiol Drug Saf. 2021; 30: 482–491. https://doi.org/10.1002/pds.5191
5	**Impact of EU label changes and pregnancy prevention programme for medicinal products containing valproate**	**Teratogenic risk, congenital malformations and neurodevelopmental disorders:**	1. To assess the extent of the influence of recommendations from regulatory authorities on patients', prescribers', and pharmacists' awareness about the risk of adverse teratogenic effects and neurodevelopmental disorders to children of women	**Completed** HMA-EMA Catalogue of Real-World Data Studies

and related substances: risk awareness and adherence (*Valproate survey*) EUPAS32405 Framework contract: EMA/2017/09/PE	• Treatment initiated and supervised by specialist in management of epilepsy, with annual treatment reviews; • Treatment only as monotherapy at lowest effective dose; • Contraindication in women of childbearing potential (WCBP) in all indications (epilepsy, bipolar disorders, prophylaxis of migraine attacks) unless pregnancy prevention programme conditions (PPP) are met; • Contraindication in pregnancy for bipolar disorders and prophylaxis of migraine attacks, and in epilepsy for use during pregnancy unless there are no suitable treatment alternatives; • Warning on contraindications and PPP conditions, i.e., assessment of the potential for pregnancy, acknowledgment of the risks of congenital malformations and neurodevelopmental disorders, the need for pregnancy testing prior to initiation and during treatment, the need to use effective contraception, the need for annual treatment reviews by a specialist, the need for specialist consultation on planning pregnancy and switching to alternative treatment options prior to conception, and before contraception is discontinued, and the need for urgent physician consultation in case of pregnancy during valproate treatment; • Warning that in case of pregnancy or pregnancy planning specialist consultation is required on switching to alternative	exposed to valproate and related substances during pregnancy, and to investigate whether knowledge, attitudes and practices have been affected. 2. To evaluate health care professionals' (physicians and pharmacists) knowledge and adherence to the PPP and RMM for WCBP intending to use medicinal products containing valproate or related substances, with a focus on receipt of and awareness about educational materials, contraindications, provision of patient cards, annual review and risk assessments and their influence on valproate exposure during pregnancy. 3. To assess patient knowledge and adherence to the PPP and RMM, with a focus on educational materials, need for pregnancy testing prior, during and after treatment initiation, use of effective contraception throughout treatment, consent for risk acknowledgment forms.

		treatment options prior to conception, and before contraception is discontinued, or before discontinuation of valproate treatment; • Boxed warning and Quick Response (QR) code in package leaflet; • Visual reminder outer package; • Healthcare professional guide; • Patient guide; • Patient reminder card; • Annual risk acknowledgment form with checklist; • DHPC; Regulatory procedure: EMEA/H/A-31/1454*		
6	**Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing oral retinoids: risk awareness and adherence** (*Retinoids survey*) EUPAS32408 Framework contract: EMA/2017/09/PE	**Teratogenic risk:** • Boxed warning outer package and on product information on teratogenic effects and contraindications, including Quick Response (QR) codes; • Contraindication in pregnant women and WCPB unless the PPP conditions are met; • Contraindication of topical retinoids (adapalene, alitretinoin, isotretinoin, tazarotene and tretinoin) in pregnancy and in women planning pregnancy; • Warning about the potential risk of neuropsychiatric disorders and addition as adverse reaction for isotretinoin and alitretinoin;	1. To determine the extent of awareness of the PPP and of the risk of teratogenic effects in WCBP and pregnant women exposed to oral retinoid containing medicinal products, by patient and by healthcare professionals, with particular focus on: 1.1 Extent of the influence of recommendations from regulatory authorities on knowledge, attitudes, and practices; 1.2 Feasibility of the contraceptive programme, including method of effective contraception and regular pregnancy testing; 2. To determine the extent of adherence to the PPP and RMM for oral retinoids intended for use in WCBP, with particular focus on the following components:	**Completed** HMA-EMA Catalogue of Real-World Data Studies

		• Warning on contraindications and PPP conditions, i.e., the need for contraception before, during and after treatment with one user-independent form or two complementary user-dependent forms, the need for regular pregnancy testing before, during and after treatment; • Prescription duration is limited to 30 days; • Patient reminder card; • Physician checklist and acknowledgement form; • Pharmacist checklist; • DHPC; For agreement at national level: • 7-day prescription validity; • Patient signature on the physician checklist/acknowledgement form; • Appointment table in patient reminder card; • Pictogram/symbol to accompany the boxed warning; • Pictogram/symbol as visual reminder on the outer package; Regulatory procedure: EMEA/H/A-31/1446*	2.1 Receipt and awareness of educational materials for patients (i.e., patient reminder card) and healthcare professionals (i.e., prescriber checklist/risk acknowledgement form, pharmacist checklist); 2.2 Use of effective contraception throughout treatment in line with sections 4.4 and 4.6 of the SmPC, including use of non-prescription or non-reimbursed contraceptives; 2.3 Performance of medically supervised pregnancy testing prior treatment initiation, repeated testing during treatment and one month after stopping treatment (for acitretin only the recommendation is periodically with 1-3 months intervals over a period of 3 years after stopping treatment), including pregnancy test results where available in Member States; 2.4 Obtaining patient signature for prescriber checklist and acknowledgment form, where implemented in Member States; 2.5 Implementation of monthly follow-up visits, repeated medically supervised pregnancy testing, limitation of prescription duration to 30-days and 7-day validity where legally possible and implemented in Member States;	
7	**Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate:**	**Teratogenic risk, congenital malformations and neurodevelopmental disorders:** • For RMM refer to study #5	1. To determine drug utilisation and prescription patterns of valproate-containing medicinal products in WCBP, and to investigate whether significant changes in prescribing patterns occurred, including:	**Completed** Abtahi, S., Pajouheshnia, R., Durán, C.E. et al. Impact of 2018 EU Risk Minimisation Measures and Revised

utilisation and prescribing trends (*Valproate DUS*) EUPAS31001 Framework contract: EMA/2017/09/PE	Regulatory procedure: EMEA/H/A-31/1454*	1.1 Prescription of medicinal products containing valproate and related substances, by indication, by incident and prevalent users, by age group, by dose, by duration and by country (or data source); 1.2 Discontinuation of medicinal products containing valproate and related substances, by indication, by age group, by dose, by reason for discontinuation, by duration and by country; 1.3 Time trends in the prescription of medicinal products containing valproates over a minimum of at least three years before the regulatory intervention in each country and, where possible, including data up to 2020; 2. To determine prescribers' compliance with recommendations included in sections 4.2, 4.3, 4.4 and 4.6 of the SmPC, by indication, by age group, by dose, by duration and by country; 3. To determine, in so far as is possible, patients' use of effective contraception in compliance with sections 4.4 and 4.6 of the SmPC for valproate-containing medicinal products, by indication, by age group, by method of contraception and by country. 4. To determine drug utilisation and prescription patterns over time for alternative antiepileptic medicines prescribed in WCBP or females becoming pregnant where medicinal products containing valproate and related substances had previously been prescribed or discontinued, by indication, by age group and by country; 5. Synthesis of the results of above objectives 1-4, to draw conclusions on the effectiveness of the 2018 RMM in terms of:	Pregnancy Prevention Programme on Utilisation and Prescribing Trends of Medicinal Products Containing Valproate: An Interrupted Time Series Study. Drug Saf 46, 689–702 (2023). https://doi.org/10.1007/s40264-023-01314-3

			5.1 Appropriate use of medicinal products containing valproate and related substances in WCBP in line with SmPC recommendations; 5.2 Appropriate use of pregnancy testing prior to treatment initiation, during treatment and after stopping treatment; 5.3 Use of effective contraception in WOBP exposed to valproate and related substances; 5.4 Incidence of pregnancies in WCBP exposed to valproate and related substances.	
8	**Impact of EU label changes and revised pregnancy prevention programme for oral retinoid-containing medicinal products: acitretin, alitretinoin and isotretinoin** (*Retinoids DUS*) EUPAS31095 Framework contract: EMA/2017/09/PE	**Teratogenic risk:** • For RMM refer to study #6 Regulatory procedure: EMEA/H/A-31/1446*	1. To determine drug utilisation and prescription patterns of oral retinoid containing medicinal products in women of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred in the pre- versus post-intervention period, including 1.1 Prescription of oral retinoid containing medicinal products, by indication (i.e., dermatological conditions including acne, psoriasis and eczema), by incident and prevalent users, by age group, by therapy duration and by data source; 1.2 Discontinuation of oral retinoid containing medicinal products, by indication, by age group, by reason for discontinuation and by data source; 1.3 Time trends in prescribing over a minimum of at least three years before the regulatory intervention and including data up to 2020; 2. To determine prescribers' compliance with recommendations included in sections 4.3, 4.4 and 4.6 of the SmPC for oral retinoid-containing	**Completed** Durán, C.E., Riera-Arnau, J., Abtahi, S., et al. Impact of the 2018 revised Pregnancy Prevention Programme by the European Medicines Agency on the use of oral retinoids in females of childbearing age in Denmark, Italy, Netherlands, and Spain: an interrupted time series analysis. Front Pharmacol 14, 1207976 (2023). https://doi.org/10.3389/fphar.2023.1207976

			medicinal products, by indication, by age group, by therapy duration and by data source; 3. To determine patients' use of effective contraception in compliance with sections 4.4 and 4.6 of the SmPC for oral retinoid containing medicinal products, by indication, by age group and by country (or data source). 4. To determine drug utilisation and prescription patterns over time for alternative medicines prescribed in women of childbearing potential and women becoming pregnant where oral retinoid containing medicinal products had previously been prescribed or discontinued, by indication, by age group and by database. 5. Based on the results of above objectives 1-4, to estimate the effectiveness of the 2018 RMM for oral retinoids in terms of: 5.1 Appropriate use of retinoid containing medicinal products in women of childbearing potential in line with SmPC recommendations; 5.2 Appropriate use of pregnancy testing prior to treatment initiation, during treatment and after stopping treatment; 5.3 Use of effective contraception in retinoid exposed women of childbearing potential; 5.4 Occurrence of pregnancies in retinoid exposed women of childbearing potential and pregnancy outcomes.	
9	**Impact of EU label changes for fluoroquinolone containing medicinal products for systemic**	**Long-lasting, disabling and potentially irreversible adverse drug reactions (muscle and joint disorders, neurologic and psychiatric disorders):**	1. To determine drug utilisation and prescription patterns of fluoroquinolone containing medicinal products over the period 2016 to 2020 by: 1.1 Estimating monthly incident drug use, stratified by on-label indications (which includes	**Completed** Ly, N.F., Flach, C., Lysen, T.S. et al. Impact of European Union Label Changes for

	and inhalation use - post-referral prescribing trends (*Fluoroquinolones DUS*) EUPAS37856 Framework contract: EMA/2017/09/PE	• Suspension of marketing authorisation for the quinolones nalidixic acid, pipemidic acid, cinoxacin and flumequine; • Removal of indications for milder, non-severe or self-limiting infections (such as pharyngitis, tonsillitis and acute bronchitis), prevention of travellers' diarrhoea, recurrent lower urinary tract infections and non-bacterial prostatitis; • Restriction of indication to last-line therapy in patients where other therapeutic options are not effective or not tolerated such as uncomplicated cystitis, acute exacerbation of chronic obstructive pulmonary disease (COPD), chronic bronchitis, community acquired pneumonia, acute bacterial sinusitis, and acute otitis media; • Warning on prolonged, disabling and potentially irreversible serious adverse drug reactions, tendonitis and tendon rupture, and peripheral neuropathy, and addition as adverse reactions; • DHPC; Regulatory procedure: EMEA/H/A-31/1452*	first line and last line indications) and off-label indications (mild infections); 1.2 Estimation of early discontinuation proportion (prescribed courses that were discontinued prior to intended treatment end date). 2. To evaluate the impact of regulatory interventions on fluoroquinolone prescribing patterns using time series analysis. 3. To determine prescribers' compliance with warnings in SmPC section 4.4, on tendinitis and tendon rupture as well as in aortic aneurysm/ dissection specifically by calculation of monthly incident prescription rates in the subgroups at risk: 3.1 Risk groups for tendinitis and tendon rupture; 3.2 Risk groups for aortic aneurysm/dissection; 3.3 Patients with recent or concomitant prescribing of systemic corticosteroids. 4. To determine monthly incident prescription rates for alternative antibiotics prescribed in patients where systemic use fluoroquinolones have previously been prescribed and later switched to another treatment.	Fluoroquinolone-Containing Medicinal Products for Systemic and Inhalation Use: Post-Referral Prescribing Trends. Drug Saf 46, 405–416 (2023). https://doi.org/10.1007/s40264-023-01286-4
10	**Impact of EU label changes for medicinal products containing methotrexate for weekly administration: risk awareness and adherence** (*Methotrexate survey*)	**Medication errors due to daily instead of weekly dosing:** • Prescription only by physicians with expertise in the use and understanding the risks related to methotrexate; • Prescriber to ensure patient compliance with once weekly regimen;	1. To determine the extent of prescriber awareness and knowledge of the risk of inadvertent overdose due to daily instead of weekly use and adherence to SmPC recommendations for oral and parenteral methotrexate (MTX) containing medicines with at least one indication requiring once-weekly dosing, with particular focus on the following elements: 1.1 Receipt and awareness of the DHPC;	**Completed** Lysen, T, Karimi, L, Wang, M, Singh, S, Toussi, M. Impact of European Union label changes to avoid inadvertent use of medicinal products containing methotrexate for once-weekly administration: A

EUPAS44827 Framework contract: EMA/2017/09/PE	• Boxed warning that the product must only be taken/used once weekly; • Visual reminder on the outer packaging to take/use the product only once a week with space to mark a weekday for intake/use; • Visual reminder on the inner packaging that the product must only be taken/used once weekly; • Switch from bottle to blister packaging; • Patient card informing on once weekly dosing regimen with space to write the day of the week; • Updated healthcare professional's checklist or guide; • DHPC; Regulatory procedure: EMEA/H/A-31/1463*	1.2 Knowledge of the dosing frequency of MTX in the treatment of inflammatory diseases (e.g., rheumatologic/dermatological diseases or Crohn's disease), by indication; 1.3 Knowledge of the updated posology instructions and boxed warning; 1.4 Receipt and awareness of the new or updated educational materials for healthcare professionals (checklist or guide) and awareness of the patient card to avoid the risk of inadvertent overdose due to daily instead of weekly use. 2. To determine the extent of pharmacist awareness and knowledge of the patient card, the visual reminder on the outer packaging and the need to mark the day of intake for indications requiring once-weekly dosing regimens, and adherence to marking the day of intake on the outer packaging. 3. To determine the extent of patient awareness and knowledge of the following elements introduced to avoid incorrect administration schedules for oral and parenteral MTX containing medicines with at least one indication requiring once-weekly dosing: 3.1 Receipt and awareness of the patient card, and knowledge of symptoms of MTX overdose and the purpose of the patient card; 3.2 Knowledge of the once-weekly dosing frequency of MTX in the treatment of inflammatory diseases, by indication; 3.3. Awareness and knowledge of the visual reminder on the packaging of oral and parenteral MTX containing products;	survey amongst prescribers, pharmacists and patients on awareness, knowledge, and behaviour. Pharmacoepidemiol Drug Saf. 2023; 1-9. https://doi.org/10.1002/pds.5692

			3.4 Awareness and knowledge of the boxed warning in the package leaflet;	
11	**Study of exposure and use patterns of alternatives to ranitidine-containing medicines in patients treated with ranitidine** (*Ranitidine DUS*) EUPAS44548 Framework contract: EMA/2017/09/PE	**Nitrosamine impurities:** • Suspension of ranitidine-containing medicinal products; Regulatory procedure: EMEA/H/A-31/1491*	1. To determine drug utilisation and prescription patterns of medicinal products containing ranitidine or alternative medicinal products by estimating incident use, stratified by quarter, referral period, indication of use, age group, sex, formulation, and by country and data source. 2. To describe switching to alternative medicinal products, covering the following product classes as a minimum: 2.1 H2-receptor antagonists on class and substance level in patients using ranitidine during the pre-referral period and switching to other H2-receptor antagonists. 2.2 Medicinal products containing proton-pump inhibitors, on class and substance level in patients using ranitidine during the pre-referral period and switching to other proton-pump inhibitors. 2.3 Other medicinal products for acid-related disorders classified by class level of the related ATC-Codes not included under 2.1 and 2.2 (e.g., use of antacids) in patients using ranitidine during the pre-referral period and switching to other substances. 3. To describe patients permanently discontinuing treatment with ranitidine-containing medicinal products without switching to alternative medicines and stratify the analysis by: quarter, referral period, prior ranitidine indication, age group, sex, prior usage patterns of ranitidine, and by country and data source.	**Completed** Arinze, J.T., de Ridder, M.A.J., Vojinovic, D. et al. Drug Utilisation Patterns of Alternatives to Ranitidine-Containing Medicines in Patients Treated with Ranitidine: A Network Analysis of Data from Six European National Databases. Drug Saf 46, 1353–1362 (2023). https://doi.org/10.1007/s40264-023-01354-9

			4. To describe drug utilisation patterns in new starters of the therapy in the set of indications, where ranitidine has been predominantly prescribed prior to suspension of ranitidine: prescribing and drug utilisation of medicinal products for treatment of the indication is described by type of drug, quarter, referral period, age group, sex, formulation, and by country and data source.	
12	**Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence** (*Covid-19 vaccines TTS survey*) EUPAS44970 Framework contract: EMA/2017/09/PE	**Thrombosis with thrombocytopenia syndrome:** • Warning on thrombosis with thrombocytopenia syndrome (TTS), and addition as adverse reaction; • Contraindication in patients who had experienced TTS following previous vaccination; • DHPC; • Regulatory communication on recommendations from learned societies for assessing signs and symptoms of TTS following vaccination Covid-19 adenovector vaccines; Regulatory procedure: EMEA/H/A-5(3)/1507#	1. To determine the extent of how regulatory actions for TTS have changed national vaccination policy, including change in risk and age group prioritization, change in recommendations for the second vaccine dose and recommendations for other SARS-CoV-2 vaccines available at the time, by country, and by vaccine brand. 2. To determine the level of healthcare professional awareness and knowledge of the risk of TTS and their adherence to SmPC recommendations for SARS-CoV-2 adenovirus vector vaccines, with particular focus on the following elements: 2.1 Receipt and awareness of the DHPC. 2.2 Knowledge and awareness of the signs and symptoms of TTS and the need for healthcare professionals to refer to specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat the condition. 2.3 Knowledge and awareness of (updated) clinical guidelines and recommendations from learned societies for treating TTS (e.g., with anticoagulants), by learned society, by country, by dissemination method and date. 2.4 Knowledge and awareness of the contraindication to use a second dose of adenovirus vaccine in patients who have	**Completed** Buhl, C., Jacobsen, R., Almarsdóttir, A.B. et al. Public's perspective on COVID-19 adenovirus vector vaccines after Thrombosis with thrombocytopenia syndrome (TTS) reports and associated regulatory actions - A Cross-Sectional Study in six EU member states. Vaccine 2024; 42: 556-563. https://doi.org/10.1016/j.vaccine.2023.12.065

			experienced TTS after a first dose vaccination with Vaxzevria. 3. To determine the extent of change in healthcare professionals´ attitudes towards COVID-19 national vaccination campaigns and recommendations, by country, by age group, and by national vaccination strategy (i.e., through vaccination centre, general practitioner, specialist etc.). 4. To determine the extent of change in citizens' attitudes towards vaccination against SARS-CoV-2, by country, by age group, by gender, and if feasible, by type of regulatory action.	
13	**Implementation of EU risk minimisation measures for medicinal products in clinical guidelines** *(RMM implementation in clinical guidelines)* EUPAS47588 Framework contract: EMA/2020/46/TDA	**RMM in the following disease areas:** 1. Neurological diseases/**Valproate** (2018)[1] : Pregnancy prevention programme (PPP); 2. Infectious diseases/**(Fluoro-)Quinolones** (2018)[2]: Restrictions in use; 3. Inflammatory, autoimmune and cancer diseases/**Methotrexate** (2019)[3]: Preventing dosing errors; 4. Diabetes/**Metformin** (2016)[4]: Monitoring kidney function; 5. Cancer diseases/**Fluorouracil** and related substances (2020)[5] : Test for lack of dihydropyrimidine dehydrogenase (DPD) before starting fluorouracil, capecitabine, tegafur or flucytosine by injection or infusion.	1. Identify and describe the key stakeholders, processes, roles, and responsibilities for updating clinical guidelines on pharmacological treatment in six European countries 2. Describe and analyse how medicinal product specific RMM for the five disease priority areas and active substances have been integrated in relevant clinical guidelines in six European countries, identifying the key elements of risk minimisation included in new or updated clinical guidelines, key milestones and enablers and barriers for updating, publication/dissemination and adoption of guidelines in healthcare practice 3. Provide recommendations for regulators to engage with healthcare professional bodies and other responsible parties to strengthen the role of clinical guidelines for RMM implementation,	**Completed** HMA-EMA Catalogue of Real-World Data Studies

[1] https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0
[2] https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products
[3] https://www.ema.europa.eu/en/medicines/human/referrals/methotrexate-containing-medicinal-products
[4] https://www.ema.europa.eu/en/medicines/human/referrals/metformin-metformin-containing-medicines
[5] https://www.ema.europa.eu/en/medicines/human/referrals/fluorouracil-fluorouracil-related-substances-capecitabine-tegafur-flucytosine-containing-medicinal

	For details on individual RMM please refer to respective regulatory procedures. Regulatory procedures: 1. EMEA/H/A-31/1454* 2. EMEA/H/A-31/1452* 3. EMEA/H/A-31/1463* 4. EMEA/H/A-31/1432* 5. EMEA/H/A-31/1481*	outlining feasible concrete steps EMA and national competent authorities could consider.

^ Study registration number in the HMA-EMA Catalogue of Real-World Data Studies (https://catalogues.ema.europa.eu), replacing the European Union electronic register of post-authorisation studies (EU PAS Register®).
$ Framework refers to EMA's framework contract procurement procedure under which the study was commissioned. Where the study was conducted collaboratively by the EMRN this is stated.
* Referral procedure under Article 31 of Directive 2001/83/EC based on the evaluation of pharmacovigilance data.
# Referral procedure under Article 5(3) of Regulation (EC) 726/2004 where the Committee for Medicinal Products for Human Use (CHMP) provides an opinion on any scientific matter concerning the evaluation of medicinal products for human use, in consultation with the Pharmacovigilance Risk Assessment Committee (PRAC).