Title: Understanding the Work of the Pharmacovigilance Risk Assessment Committee (PRAC): A Quantitative Review of the Post-Authorisation Safety Evaluation of Antidiabetic Drugs from 2012 to 2022

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Table S1 Active pharmaceutical ingredients (APIs) and ATC list

ATC (code) [a]	Drug-class	Active pharmaceutical ingredients (APIs)
3rd level, pharmacological subgroup		
Insulins and analogues (A10A)	Insulin	Insulin aspart; Insulin bovine; Insulin degludec; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin human; Insulin human (rDNA); Insulin lispro; Insulin porcine; Insulin analogue human recombinant [b]; Insulin [b]
4th level, chemical subgroup		
Biguanides (A10BA)	Biguanides	Metformin
Sulfonylureas (A10BB)	Sulfonylureas	Carbutamide; Glibenclamide; Gliclazide; Glimepiride; Glipizide; Gliquidone; Tolbutamide
Alpha glucosidase inhibitors (A10BF)	Alpha glucosidase inhibitors	Acarbose; Miglitol
Thiazolidinediones (A10BG)	Thiazolidinediones	Pioglitazone; Rosiglitazone
Dipeptidyl peptidase 4 (DPP-4) inhibitors (A10BH)	DPP-4	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin; Vildagliptin
Glucagon-like peptide-1 (GLP-1) analogues (A10BJ)	GLP-1	Albiglutide; Dulaglutide; Exenatide; Liraglutide; Lixisenatide; Semaglutide
Sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK)	SGLT2	Canagliflozin; Dapagliflozin; Empagliflozin; Ertugliflozin; Sotagliflozin
Other blood glucose lowering drugs, excl. insulins (A10BX)	Other antidiabetic	Nateglinide; Repaglinide

[a] ATC A10BD (Combinations of oral blood glucose-lowering drugs) are excluded since PRAC discussion always focused on singular APIs, and the medicinal products of fixed-combination share the same PSURs procedure with corresponding singular API.

[b] APIs don't have the same terminology in the ATC system, where it is mainly based on the duration of insulin action

Table S2 The Pharmacovigilance Assessment Committee (PRAC) procedures and activities included/excluded in the study, the table follows the heading structure of the PRAC meeting minutes.

Fixed headings in PRAC meeting minutes	Criteria
1. Introduction	Exclude
2. EU referral procedures for safety reasons: urgent EU procedures	
2.1 Newly triggered procedures	Include
2.2 Ongoing procedures	Include
2.3 Procedures for finalisation	Include
3. EU referral procedures for safety reasons: other EU referral procedures	
3.1 Newly triggered procedures	Include
3.2 Ongoing procedures	Include
3.3 Procedures for finalisation	Include
3.4 Re-examination procedures	Include
3.5 Others	Include
4. Signals assessment and prioritisation	
4.1 New signals detected from EU spontaneous reporting systems	Include
4.2 new signals detected from other sources	Include
4.3 Signals follow-up and prioritisation	Include
5. Risk management Plan (RMPs)	
5.1 Medicines in the pre-authorisation phase	Exclude
5.2 Medicines in the post-authorisation phase - PRAC-led procedures	Include
5.3 Medicines in the post-authorisation phase - CHMP-led procedures	Include
6. Periodic safety update reports (PSURs)	
6.1 PSUR signal assessment(PSURA) procedures including centrally authorised products (CAPs) only	Include
6.2 PSUR signal assessment(PSURA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)	Include
6.3 PSUR signal assessment(PSURA) procedures including nationally authorised products (NAPs)	Include
6.4 Follow-up PSUR/PSUSA procedures	Include
7. Post-authorisation safety studies (PASS)	
7.1 Protocols of PASS imposed in the marketing authorisation(s)	Exclude
7.2 Protocols of PASS non-imposed in the marketing authorisation(s)	Exclude
7.3 Results of PASS imposed in the marketing authorisation(s)	Include
7.4 Results of PASS non-imposed in the marketing authorisation(s)	Include
7.5 Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation	Include
7.6 Others	Exclude
7.7 New Scientific Advice	Exclude
7.8 Ongoing Scientific Advice	Exclude
7.9 Final Scientific Advice (Reports and Scientific letters)	Exclude
8. Renewals of the marketing authorisation, conditional renewal and annual reassessments	
8.1 Annual reassessments of the marketing authorisation	Include
8.2 Conditional renewals of the marketing authorisation	Include
8.3 Renewals of the marketing authorisation	Include
9. Product related pharmacovigilance inspections	Exclude
10. Other safety issues for discussion requested by the CHMP or the EMA	
10.1 Safety related variations of the marketing authorisation	Include
10.2 Timing and message content in relation to Member States' safety announcement	Exclude
10.3 Other requests	Include
10.4 Scientific Advice	Exclude
11.Other safety issues for discussion requested by the Member States	
11.1 Safety related variations of the marketing authorisation	Include
11.2 Other requests	Include
12. Organisational, regulatory and methodological matters	Exclude

13. Any other business	Exclude

In addition, headings and subheadings in Annex I corresponding to include headings listed above were also included in the study. Annex II, Annex III and explanatory notes were excluded. The heading numbering could slightly change during the study period from 2012 to 2022.

Table S3: Information collected in eligible PRAC procedures/activities from 2012 to 2022.

1. The date of the PRAC meeting where the procedure/activities events occur.
2. The fixed headings of the PRAC procedure/activity, which contains information on Signal management procedures (Referral, Signal Procedure, PSURs, MA renewal and Other safety issues) or oversight activities (RMP, PASS).[a]
3. The antidiabetic API(s) and their corresponding safety concerns/signals. [a]
4. Special population-related safety concerns/signals, including elderly, patients with comorbidities, paediatric, pregnancy, or drug interaction/co-administration.
5. Recommendations for regulatory actions, categorised as SmPC variations, RMP updates, implementation/removal/update of additional RMMs, referral recommendations, conduct a new PASS study, withdrawal, or determination that no regulatory action is currently needed.
6. EMA procedure codes identified in discussion events.
7. Identified information of evidence referenced in the PRAC discussion.

[a] Details listed in Table S1 and S2 in the electronic supplemental material [ESM].

Table S4: Simplified examples of situations that could constitute a drug-AE evaluation

Evaluation spanning multiple meetings within the same procedure type	Linagliptin-Arthralgia • The signal was addressed by PRAC under the "Signal assessment and prioritisation" procedure (PRAC Meeting Minutes, October 5, 2015). • During the October 2015 meeting, PRAC determined that the signal required further evaluation. It was recommended that additional information be requested from the marketing authorisation holder (MAH) within a 60-day timeframe. This additional information was to undergo assessment, leading to a subsequent PRAC recommendation within a 90-day timeframe. • Five months later, the signal was concluded under the "Signal assessment and prioritisation" procedure (PRAC Meeting Minutes, February 8, 2016).
Evaluation spanning multiple meetings within different procedure types	Pioglitazone-Lactic acidosis • The signal was initially identified through the PASS procedure (PRAC Meeting Minutes, September 26, 2016) However, lactic acidosis was not mentioned in this procedure. We documented it later based on a subsequent update of the risk management plan (RMP), as described below, based on the following EMA procedure numbers: *Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS0991/0075; GLUSTIN (CAP) - EMEA/H/C/000286/WS0991/0073 pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/WS0991/0051 pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS0991/0062; GLUBRAVA (CAP) - EMEA/H/C/000893/WS0991/0047* • Subsequently, the RMP was updated, as documented in the RMP procedure (PRAC Meeting Minutes, November 27, 2017): *"In addition, the RMPs for Competact and Glubrava, are updated to include the lactic acidosis questionnaire as requested in the conclusions of variations EMEA/H/C/000655/WS0991/0062 and EMEA/H/C/000893/WS0991/0047 adopted in January 2017".* However, since lactic acidosis was not mentioned in the PRAC meeting minutes of Jan 9, 2017, we categorised this evaluation under two procedures that included clear signal information.
Multiple evaluations for the same drug-AE pair	Exenatide-Hepatic enzyme increased • The signal was first identified in PRAC minutes under the PSUR procedure in 2013 (PRAC Meeting Minutes, October 7, 2013), recommending that " *In the next PSUR, the MAH should provide a detailed review of injection site abscess/ cellulitis and a review of increased liver enzymes, and should consider updating the product information accordingly."* • Subsequently, it re-emerged during another PSUR procedure in 2014 (PRAC Meeting Minutes, May 5, 2014), with a similar recommendation regarding this signal to previous PSURs: *"In the next PSUR, the MAH should provide a detailed review of cases of increased liver enzymes and of cases of cholecystitis/cholelithiasis and propose an update of the product information as warranted."*

Table S5 List of drug-AE pairs discussed in the PRAC (2012-2022)

Medical event	Number	Drug(s) related to AEs
Blood and lymphatic system disorders		
Thrombocytopenia	1	Sitagliptin
Haemolytic anaemia	1	Glibenclamide
Blood dyscrasias	1	Pioglitazone
Anaemia megaloblastic	1	Metformin
Cardiac disorders		
Palpitations	1	Saxagliptin
Major cardiovascular events [f]	1	Saxagliptin
MACE [f]	1	Alogliptin
Cardiovascular safety [f]	4	Empagliflozin;Insulin degludec,Linagliptin;Sitagliptin
Cardiovascular morbidity [f]	1	Insulin Group[e]
Cardiovascular disorder	1	Liraglutide
Cardiac failure	4	Alogliptin;Linagliptin;Pioglitazone;Saxagliptin
Cardiac Events [f]	1	Exenatide
Atrial fibrillation	1	Pioglitazone
Arrhythmia	2	Exenatide;Glibenclamide
Ear and labyrinth disorders		
Meniere's disease	1	Albiglutide
Endocrine disorders		
Goitre	1	Exenatide
Eye disorders		
Refraction disorder	1	Insulin human
Macular oedema	1	Pioglitazone
Diabetic retinopathy	1	Insulin human
Gastrointestinal disorders [a]		
Rectal haemorrhage	1	Exenatide
Pancreatitis acute	7	Canagliflozin;Dulaglutide;Empagliflozin;Exenatide;Linagliptin;Lixisenatide;Semaglutide
Pancreatitis	11	Alogliptin;Canagliflozin;Dapagliflozin;DPP4[e];Dulaglutide;Empagliflozin;Exenatide;GLP1[e];Liraglutide;Pioglitazone;Saxagliptin
Intestinal stenosis	1	Vildagliptin
Intestinal obstruction	3	Alogliptin;Sitagliptin;Vildagliptin
Impaired gastric emptying	4	Dulaglutide;Exenatide;Insulin glargine,lixisenatide;Liraglutide
Gastrointestinal stenosis	3	Dulaglutide;Exenatide;Liraglutide
Gastrointestinal haemorrhage	1	Exenatide
Gastrointestinal disorder	1	Alogliptin
Diarrhoea	2	Liraglutide;Saxagliptin
Constipation	1	Saxagliptin
Abdominal pain	1	Saxagliptin
General disorders and administration site conditions		
Oedema peripheral	1	Pioglitazone
Oedema	1	Insulin human
Obstruction	3	Dulaglutide;Exenatide;Liraglutide
Injection site reaction	2	Exenatide;Insulin lispro
Fatigue	1	Liraglutide

Death	1	Insulin lispro
Cardiovascular mortality and/or all-cause mortality [f]	1	Glibenclamide
All-cause mortality [f]	1	Saxagliptin
Hepatobiliary disorders		
Liver injury	2	Dapagliflozin;Empagliflozin
Liver disorder	5	Dapagliflozin;Dulaglutide;Exenatide;Metformin;Saxagliptin
Hepatotoxicity	1	Alogliptin
Hepatic impairment	1	Liraglutide
Hepatic failure	1	Glibenclamide
Hepatic events [f]	2	Alogliptin;Pioglitazone
Drug-related hepatic disorders*	1	Insulin degludec
Cholelithiasis	4	Dulaglutide;Exenatide;Insulin degludec,liraglutide;Liraglutide
Cholecystitis	4	Dulaglutide;Exenatide;Insulin degludec,liraglutide;Liraglutide
Biliary tract disorder	1	Lixisenatide
Acute hepatic failure	1	Saxagliptin
Immune system disorders		
Hypersensitivity	10	Albiglutide;Alogliptin;Canagliflozin;Dapagliflozin;Dulaglutide;Empagliflozin;Insulin human;Insulin lispro;Saxagliptin;Semaglutide
Anaphylactic reaction	3	Dulaglutide;Insulin aspart;Insulin human
Infections and infestations		
Vulvovaginal candidiasis	1	Canagliflozin
Urosepsis	2	Dapagliflozin;Empagliflozin
Urogenital infection fungal	1	Canagliflozin
Urinary tract infection	3	Canagliflozin;Dapagliflozin;Empagliflozin
Pyelonephritis	2	Dapagliflozin;Empagliflozin
Opportunistic infection	1	Saxagliptin
Injection site cellulitis	1	Exenatide
Injection site abscess	1	Exenatide
Infection	2	Alogliptin;Saxagliptin
Genital infection	1	Empagliflozin
Fungal infection	1	Canagliflozin
Fournier's gangrene	1	SGLT2 [e]
Diverticulitis	1	Albiglutide
Appendicitis	1	Albiglutide
Injury; poisoning and procedural complications		
Overdose	1	Liraglutide
Fracture	3	Canagliflozin;Empagliflozin;Pioglitazone
Foetal exposure during pregnancy	2	Glibenclamide;Metformin
Carcinogenicity	1	Sitagliptin
Investigations		
Lymphocyte count decreased	1	Saxagliptin
Lipase increased	2	Insulin degludec,liraglutide; Liraglutide
Hepatic enzyme increased	1	Exenatide
Heart rate increased	1	Liraglutide
Haematocrit increased	1	Dapagliflozin

Glomerular filtration rate decreased	1	Empagliflozin
Blood glucose increased	1	Insulin degludec,liraglutide
Blood creatinine increased	1	Empagliflozin
Amylase increased	2	Insulin degludec,liraglutide;Liraglutide
Metabolism and nutrition disorders [b]		
Vitamin B12 deficiency	1	Metformin
Lactic acidosis	2	Metformin;Pioglitazone
Hypoglycaemia	12	Canagliflozin;Glibenclamide;Gliclazide;Glimepiride;Glipizide;Gliquidone;Insulin human;Insulin lispro;Liraglutide;Repaglinide;Tolbutamide
Hyperglycaemia	1	Insulin degludec,liraglutide
Dysglycaemia [f]	1	Insulin Group[e]
Diabetic ketoacidosis(off-lable use in T1D)	1	Canagliflozin
Diabetic ketoacidosis(in T1D indication extension)	1	Dapagliflozin
Diabetic ketoacidosis	8	Canagliflozin;Dapagliflozin;Empagliflozin;Ertugliflozin;GLP1[e];Saxagliptin;Semaglutide;SGLT2[e]
Device-associated hyperglycaemia and hypoglycaemia [f]	1	Exenatide
Dehydration	1	Dulaglutide
Decreased appetite	1	Albiglutide
Musculoskeletal and connective tissue disorders		
Tendonitis	1	Glibenclamide
Rhabdomyolysis	3	DPP4[e];Sitagliptin;Vildagliptin
Myositis	1	Dapagliflozin
Myopathy/muscle events [f]	1	Vildagliptin
Myopathy	1	Dapagliflozin
Myalgia	1	Vildagliptin
Muscular weakness	1	Dapagliflozin
Muscle atrophy	1	Dapagliflozin
Arthropathy	1	Sitagliptin
Arthralgia	2	Alogliptin;Linagliptin
Neoplasms benign, malignant and unspecified [c]		
Urinary tract malignancies [f]	1	Empagliflozin
Thyroid neoplasm	1	Exenatide
Thyroid cancer	4	Albiglutide;Exenatide;Lixisenatide;Vildagliptin
Renal cell carcinoma	1	Canagliflozin
Renal cancer	2	Canagliflozin;Empagliflozin
Prostate cancer	1	Pioglitazone
Pancreatic carcinoma	10	Albiglutide;Dulaglutide;Exenatide;Liraglutide;Lixisenatide;Pioglitazone;Saxagliptin;Semaglutide;Sitagliptin;Vildagliptin
Non-bladder urological tumours [f]	1	Pioglitazone
Non-bladder malignancy [f]	1	Pioglitazone
Neoplasm malignant	5	Albiglutide;Dapagliflozin;Glibenclamide;Insulin detemir;Insulin Group[e]
Neoplasm	4	Insulin lispro;Liraglutide;Pioglitazone;Sitagliptin
Medullary thyroid cancer	3	Dulaglutide;GLP1[e];Lixisenatide
Malignant melanoma	1	Liraglutide

Cholangiocarcinoma	2	DPP4[e];GLP1[e]
Breast cancer	3	Insulin glargine;Liraglutide;Vildagliptin
Bladder cancer	2	Canagliflozin;Pioglitazone
Nervous system disorders		
Neuropathy peripheral	1	Insulin human
Headache	1	Liraglutide
Encephalopathy	2	Glibenclamide;Metformin
Dystonia	1	Glibenclamide
Psychiatric disorders		
Suicide attempt	1	Metformin
Neuropsychological symptoms	1	Vildagliptin
Depression	1	Vildagliptin
Renal and urinary disorders		
Tubulointerstitial nephritis	3	Alogliptin;Dapagliflozin;Empagliflozin
Severe complication of Urinary tract infection [f]	2	Dapagliflozin;Empagliflozin
Renal safety [f]	1	Dapagliflozin
Renal injury	1	Canagliflozin
Renal impairment	4	Canagliflozin;Dapagliflozin;Dulaglutide;Liraglutide
Renal failure	3	Canagliflozin;Dulaglutide;Vildagliptin
Renal and urinary disorders	2	Exenatide;Saxagliptin
Nephritis	1	Dapagliflozin
Chronic kidney disease	2	Dulaglutide;Empagliflozin
Acute kidney injury	8	Albiglutide;Dapagliflozin;Dulaglutide;Empagliflozin;Exenatide;Glibenclamide;Saxagliptin;Vildagliptin
Reproductive system and breast disorders		
Balanoposthitis	1	Canagliflozin
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	1	Canagliflozin
Interstitial lung disease	1	Vildagliptin
Skin and subcutaneous tissue disorders [d]		
Urticaria	2	Empagliflozin;Insulin human
Toxic epidermal necrolysis	1	Exenatide
Stevens-Johnson syndrome	2	Canagliflozin;Dapagliflozin
Skin reaction	5	Alogliptin;Canagliflozin;Exenatide;Metformin;Pioglitazone
Skin lesion	1	Saxagliptin
Severe cutaneous adverse reaction	2	Alogliptin;Canagliflozin
Rash	3	Dapagliflozin;Empagliflozin;Insulin human
Photosensitivity reaction	2	Canagliflozin;Glibenclamide
Pemphigus	1	Glibenclamide
Pemphigoid	7	Alogliptin;Empagliflozin;Glibenclamide;Linagliptin;Saxagliptin;Sitagliptin;Vildagliptin
Nodular vasculitis	1	Dapagliflozin
Lipodystrophy acquired	2	Insulin glargine, lixisenatide; Insulin human
Erythema multiforme	1	Alogliptin
Cutaneous vasculitis	2	Metformin;Vildagliptin
Cutaneous amyloidosis	4	Insulin glargine;Insulin glargine,lixisenatide;Insulin Group;Liraglutide

Angioedema	8	Canagliflozin;Dapagliflozin;Dulaglutide;Empagliflozin; Glibenclamide;Semaglutide;Sitagliptin;Vildagliptin
Social circumstances		
Elderly	5	Canagliflozin;Dulaglutide;Lixisenatide;Metformin;Saxagliptin
Surgical and medical procedures		
Limb amputation	3	Dapagliflozin;Ertugliflozin;SGLT2[e]
Vascular disorders		
Embolism	1	Empagliflozin

DPP-4i dipeptidyl peptidase 4 inhibitors; *GLP-1RA* glucagon-like peptide-1 receptor agonist; *MACE* Major adverse cardiac events; *SGLT-2i* sodium-glucose transport protein-2 inhibitor

[a] Acute and non-acute pancreatitis were the most common safety signals linked to second-generation antidiabetics.

[b] Most prevalent in hypoglycemia, particularly in connection with Sulfonamides.

[c] Pancreatic carcinoma (N=6) and thyroid cancer (N=8) were frequently discussed with GLP-1 agonists. Urinary tract malignancies with SGLT2 inhibitors (N=5).

[d] Eight pairs were related to cutaneous amyloidosis, with three connected to insulin use.

[e] 14 pairs associated with drug class, three each were related to SGLT-2i and DPP-4i, and four each to GLP-1RA and Insulin

[f] Not preferred terminology of MedDRA, a definition based on PRAC meeting minutes text

Table S6 PRAC safety Evaluations related to antidiabetics between 2012 and 2022, which were evaluated through a referral procedure or where the evaluation took place in connection with more than one type of procedure/activity.

Evaluation	Duration	Details
GLP-1RA and DPP-4 inhibitors - pancreatitis	2013-2014	• In 2013, EMA identified the signal based on findings from Butler. et al. study, suggesting the pancreatitis risk of GLP-1 based therapies (GLP-1 and DPP4) among patients with type 2 diabetes (T2D). Later, the **evaluation started** in the *referral procedure* directly. (PRAC meeting 2013.04.11) • In October 2013, PRAC **recommended a type II variation,** and update of the SmPC and risk management plan (RMP). (PRAC meeting 2013.10.07) • In 2014, the *RMP procedure* implemented the updates without details documented in PRAC minutes. (PRAC meeting 2014.04.07 & 2014.06.10 & 2014.09.08)
Metformin - Lactic acidosis	2015-2018	• In 2015, **a discussion was initiated** in the *PSURs procedure* due to discrepancies in the SmPC concerning metformin usage among patients with reduced kidney function across the EU. (PRAC meeting 2015.11.30) • PRAC subsequently **referred the evaluation** to a *Referral procedure*, ultimately concluding that metformin may benefit patients with T2D and moderate renal impairment, while it remains contraindicated for those with severe renal dysfunction. • In 2016, PRAC **recommended routine and additional RMMs** based on the discussion in the referral procedure (PRAC meeting 2016.01.25), including: 1) Marketing Authorisation Holders (MAHs) were instructed to monitor and analyse future cases of lactic acidosis and report these findings in upcoming PSURs. 2) The communication was disseminated to healthcare professionals (DHPC) and patients, accompanied by an updated SmPC to reflect this extended indication. 3) All product information for metformin-containing drugs in the EU must be updated to align with the new recommendations. • Corresponding updates were made to the *RMP*. (PRAC meeting 2017.02.06 & 2017.04.03 & 2017.06.06) • **For ongoing monitoring**, in 2018 *PSURs* for the sitagliptin/metformin fixed-dose combination will include a review of lactic acidosis cases. (PRAC meeting 2018.03.05)
SGLT-2 inhibitors - Diabetic ketoacidosis (DKA)	2015-2022	• **The first evaluation initiated** from the *Signal assessment and prioritisation* procedure following a safety warning issued by the FDA in 2015, concluded that the **distribution of a DHPC** alongside a communication plan is necessary, with the evaluation **transit to the Referral procedure**. (PRAC meeting 2015.06.08) • The evaluation concluded in February 2016 through the *Referral procedure*, **resulting in the following regulatory actions**: 1) **Add atypical diabetic ketoacidosis (DKA) to the SmPC** (PRAC meeting 2016.02.08) 2) **Updates** to ongoing and planned activities in the ***RMP*** (PRAC meeting 2016.08.30 & 2016.10.24 & 2016.11.28) • During the corresponding Type II variation process, the term "and fatal" was added to the warning for canagliflozin. However, the **previous referral's evidence was deemed insufficient to apply this fatal terminology** to all SGLT2 inhibitors. Hence, the Committee for Medicinal Products for Human Use (CHMP) requested PRAC to provide advice, leading to *the signal re-emerging in the procedure "Other safety issues from CHMP".* (PRAC meeting 2017.03.06) Following further discussion in 2017, PRAC recommended: 1) Revising the warnings for canagliflozin-containing medicines to include fatal cases, and the revised warning should be added to other SGLT2 products as well. 2) Further evaluation of fatal DKA cases for other SGLT2 inhibitors in upcoming PSURs. • Canagliflozin's **RMP was updated** following the latest recommendations from PRAC, as informed in previous evaluations and PSURs. (PRAC meeting 2017.08.29) • An interim report of a **PASS study focusing on the DKA** risk associated with empagliflozin was submitted to the *RMP* in 2018. This study was requested and discussed by the FDA and PRAC. (PRAC meeting 2018.03.05) • The final report of this 5-year enhanced pharmacovigilance study was submitted and documented in the *PASS procedure* in 2022, with corresponding **updates made**

		to the RMP (no further details about the RMP update were provided by PRAC). (PRAC meeting 2019.04.08 & 2020.03.09 & 2021.03.08 & 2022.04.04) • **The second evaluation** was initiated in 2019 in the *Signal assessment and prioritisation* procedure after EMA identified new information regarding DKA in surgical patients in EudraVigilance databases as well as following a discussion with the FDA. After deliberation, PRAC recommended the **product information be updated** to include this new safety knowledge. (PRAC meeting 2019.03.12 & 2019.09.02) ➢ In parallel with the first evaluation and the new PASS study, dapagliflozin was granted an extended indication for use in Type 1 Diabetes (T1D) in 2018. As a part of this indication extension, RMMs related to DKA in T2D patients were extended to T1D patients, the RMP was updated, and educational materials regarding DKA were provided to T1D patients. (PRAC meeting 2018.10.01) ➢ Upon the removal of the T1D indication, the corresponding educational materials and imposed post-authorisation safety study (PASS) requirements were also withdrawn. (PRAC meeting 2021.08.30)
SGLT-2 inhibitors - Limb amputation(LA)	2016-2022	• **Signal was detected** in a PASS study in 2016, prompting the initiation of an evaluation through the *Signal assessment and prioritisation procedure*. After discussion, PRAC concluded that the evaluation should be *transit to the Referral procedure* to investigate if it is a class-wide issue, and MAH should **distribute a DHPC to inform the risk of the event.** (PRAC meeting 2016.04.10) • **Signal evaluation** continued to discuss if the event is a class-wise issue, and discussions of the same signal in dapagliflozin and empagliflozin were initiated in the *"Other safety issue from EMA" procedure*. (PRAC meeting 2016.06.06 & 2016.07.02) • Based on the conclusion in the previous discussion, PRAC *transits the evaluation to the Referral procedure,* extending the assessment to the entire SGLT2 drug class. In 2017, PRAC **mandated updates to the SmPC for SGLT2 inhibitors due to LA signals, and the initiation of further investigations through a new PASS study.** (PRAC meeting 2016.07.04 & 2017.02.06 & 2017.08.29) • To further **implement the regulatory actions**, the *RMP procedure* documented the corresponding update in RMPs of SGLT2 inhibitors. The analysis plan of a PASS study using a meta-analysis of three clinical trials was documented in the *PASS procedure*. (PRAC meeting 2017.09.25 & 2017.11.27) • **For Continuous monitoring**, the RMP was updated as the PASS study reached milestones within the *PASS procedure*, culminating in a conclusive update presented in the *RMP procedure*. (PRAC meeting 2018.05.14 & 2019.04.08 & 2019.10.28 & 2020.03.09 & 2020.05.11) In an independent *PSUR procedure*, ertugliflozin's product information was updated based on PRAC recommendations, incorporating new clinical data on factors increasing amputation risk. (PRAC meeting 2019.01.14) • **Regulatory action based on updated knowledge** from the latest PASS study findings. PRAC advised removing LA safety concerns from the RMP for dapagliflozin while retaining and enhancing product warnings with meta-analysis data in 2022. (PRAC meeting 2022.09.26)
Saxagliptin - Acute kidney injury	2015-2017	• **Signal detected** in 2015 in the first interim analysis of the *PASS study* focusing on the risk of hospitalization with acute kidney injury (PRAC meeting 2015.04.15) • With supportive evidence from EudraVigilance later, the evaluation *transits to Signal assessment and prioritisation* **for further evaluation**, *parallel with further PASS analysis*. (PRAC meeting 2015.07.06) • **Reached to conclusion** in *Signal assessment and prioritisation* in 2016, that no regulatory action was considered at the time of evaluation with results of the current PASS study awaited. (PRAC meeting 2016.01.11) New evaluations • In 2016, **a new PASS study** focusing on acute kidney injury evaluation started in the *PASS procedure*. (PRAC meeting 2016.08.16) • In 2017, **RMP was updated** based on the result of this PASS study, without further update details in PRAC meeting minutes. (PRAC meeting 2017.01.09 & 2017.05.02)

Among the five evaluations including a referral procedure, four addressed drug class signals, while one focused on discrepancies in the SmPC for metformin concerning lactic acidosis risk across the EU. Of four evaluations across more than 2 procedures/activities types, three pertained to referral procedures.

AE adverse event*, aRMM* Additional risk minimisation measures*, CHMP* Committee for Medicinal Products for Human Use *EMA* European Medicines Agency*, MA renewal* Renewals of the marketing authorisation, conditional renewal and

annual reassessments, *Other safety issue* Other safety issues for discussion requested by the CHMP or the EMA, *PASS* Post-Authorisation Safety Studies*, PSURs* Periodic Safety Update Reports*, RMP* Risk Management Plan

DPP-4i dipeptidyl peptidase 4 inhibitors; *GLP-1RA* glucagon-like peptide-1 receptor agonist; *SGLT-2i* sodium-glucose transport protein-2 inhibitor

Table S7 Summary of regulatory actions recommended in drug-AE evaluations related to antidiabetics in PRAC from 2012 to 2022

Type of regulatory action	Evaluations	
	n	(%)
Total	*413*	
No regulatory action	*197*	*(47.7%)*
Evaluation where the recommendation(s) for regulatory action was given in one meeting	*204*	*(49.4%)*
SmPC update	88	(21.3%)
RMP update	79	(19.1%)
PASS	1	(0.2%)
RMP update + SmPC update	33	(8.0%)
RMP update + aRMM	3	(0.7%)
Evaluations where recommendations for regulatory actions were given across more than one meeting	*12*	*(2.9%)*
RMP update → SmPC update	4	(1.0%)
RMP update → PASS	1	(0.2%)
SmPC update → RMP update	2	(0.5%)
SmPC update → aRMM	2	(0.5%)
(aRMM + Referral) → (RMP update + SmPC update)	2	(0.5%)
Referral → (SmPC update + aRMM) → RMP update	1	(0.2%)

An evaluation may result in a recommendation for one or more regulatory actions. These recommendations may be put forward in a single meeting or across multiple meetings single meeting conclusion or multiple conclusions across several meetings. For each evaluation, we recorded the first occurrence of each distinct regulatory action, whether recommended individually or combined with others in a single meeting conclusion. If no regulatory action was identified in any PRAC meeting connected with an evaluation, the outcome of the evaluation was classified as 'no regulatory action'. This table indicates that the recommendation given in separate meetings, and the recommendation for regulatory actions originated from the same meeting

aRMM Additional risk minimisation measure; *PASS* Post-Authorization Safety Studies; *RMP* Risk management plan; *SmPC* Summary of product characteristics

Table S8 PRAC Evaluations safety evaluation for antidiabetic between 2012 and 2022 where additional Risk Minimisation Measures (aRMMs) or Post-authorisation safety studies (PASS) were recommended.

	Evaluation	Details
One aRMM or PASS	Exenatide - Pancreatic carcinoma	Introducing an additional PASS study to monitor the risk of pancreatic carcinoma associated with exenatide.
	Exenatide - Hyperglycaemia/Hypoglycaemia	Conducting a PASS study to assess the effectiveness of new instructions for use (IFU) addressing incorrect device use.
	SGLT-2is - Fournier's gangrene	Distributing DHPC on the risk of Fournier's gangrene associated with SGLT2.
	Insulin Group-dysglycaemia	Implementing educational programmes to inform patients and HCPs about updates in the SmPC related to dysglycaemia risk in the insulin group.
aRMM or PASS study recommended together with other regulatory actions		
With SmPC update	Metformin-Lactic acidosis	Disseminating a DHPC and patient communications, along with an updated SmPC to incorporate the new safety information.
With referral	SGLT-2is - Limb amputation	After detecting the signal, PRAC concluded that a DHPC was needed and that the evaluation should proceed to the Referral procedure.
	SGLT-2is - Diabetic ketoacidosis	The initial discussion concluded that a DHPC should be distributed alongside a communication plan and that a Referral procedure is needed.
With RMP update	Dapagliflozin - Diabetic ketoacidosis	1) In the type II variation for indication extension to T1D, the DHPC and RMP updates initially related to T2D were extended to include T1D. 2) Due to the removal of the T1D indication, the corresponding aRMM and RMP were also removed.
	Insulin lispro - Hypersensitivity	In evaluating the variation application due to a new manufacturing process, PRAC concluded that RMP should be updated, and the communication letter issued.

aRMM Additional risk minimisation measure; *DHPC* Direct Healthcare Professional Communication ; *DPP-4i* dipeptidyl peptidase 4 inhibitors; *GLP-1RA* glucagon-like peptide-1 receptor agonist; *HCP* Health Care professionals; *PASS* Post-Authorization Safety Studies; *RMP* Risk management plan; *SGLT-2i* sodium-glucose transport protein-2 inhibitor; *SmPC* Summary of product characteristics; *T1D* Type 1 diabetes; *T2D* Type 2 diabetes

* In GVP module XVI rev 2 and rev1, the DHPC was considered an aRMM, with the newest revision 3 from August 2024 the DHPC is now considered a communication tool.

Table S9 PRAC safety Evaluations with multiple meeting conclusions where the regulatory recommendation was made across multiple meetings.

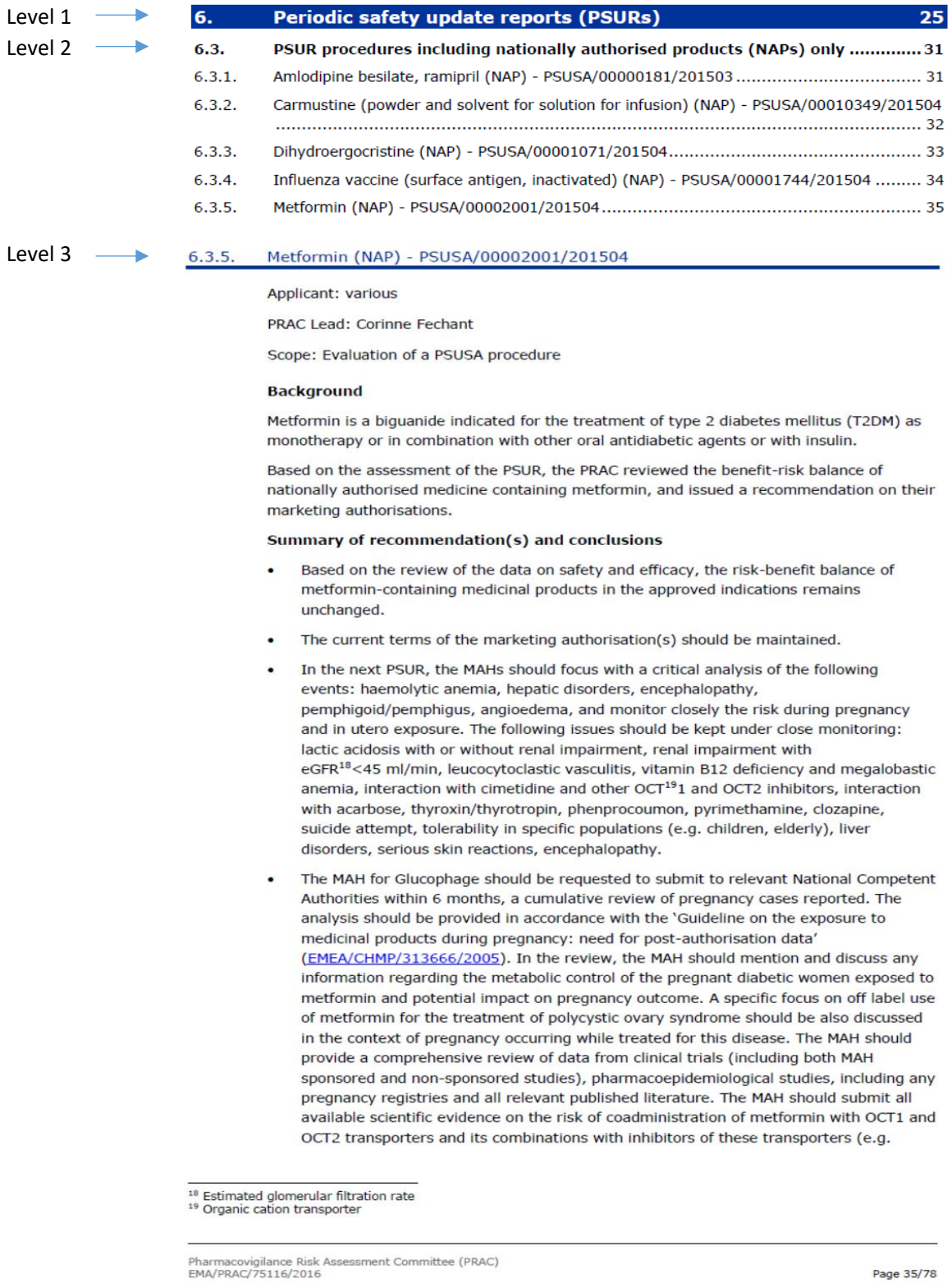
Evaluation	PSURs [a]	Referral [a]	Signal assessment and prioritisation [of a]	RMP [a]	PASS [a]
Metformin - Lactic acidosis	Referral (1)	SmPC+aRMM(2)		RMP update(3)	
Sitagliptin - Pemphigoid	SmPC(1)			RMP update(2)	
Vildagliptin - Rhabdomyolysis			SmPC (1);RMP update(2)		
Alogliptin - MACE				RMP update(1);SmPC(2)	
Saxagliptin - Cardiac failure				RMP update(1);SmPC(2)	
Exenatide - Pancreatic carcinoma				aRMM(2)	RMP update(1)
Dulaglutide - Impaired gastric emptying					RMP update(1);SmPC(2)
Pioglitazone - Bladder cancer				RMP update(1);SmPC(2)	
SGLT-2is - Diabetic ketoacidosis		RMP update+SmPC(2)	aRMM+referral (1)		
SGLT-2is - Limb amputation		RMP update+SmPC(2)	aRMM+referral (1)		
SGLT-2is - Fournier's gangrene			SmPC(1);aRMM (2)		
Insulin Group - Dysglycaemia			SmPC(1);aRMM (2)		

In the table, (1) means the first recommendation of the evaluation, (2) means the second recommendation of evaluation, (3) means the third conclusion of evaluation

aRMM Additional risk minimisation measure; *MACE* Major adverse cardiac events; *PASS:* Post-Authorization Safety Studies; *RMP* Risk management plan; *SGLT-2i* sodium-glucose transport protein-2 inhibitor; *SmPC* Summary of product characteristics

PRAC procedures or oversight activities where the conclusion was generated

Figure S1 Screenshot from a PRAC meeting minute showing an example of one PRAC regulatory procedure/activity example. Level 1: Fixed headings containing PRAC procedure or activity type information. Level 2: Fixed headings with detailed information of Level 1. Level 3: Subheading including name of the Active pharmaceutical ingredient (API)documents the involving APIs evaluated in under each PRAC-led regulatory procedure/activity. This is what we consider one PRAC procedure/activity in our analysis.



cimetidine, dolutegravir, crizotinib, olaparib, daclatasvir, vandetanib) including a proposal for a variation to update the product information.

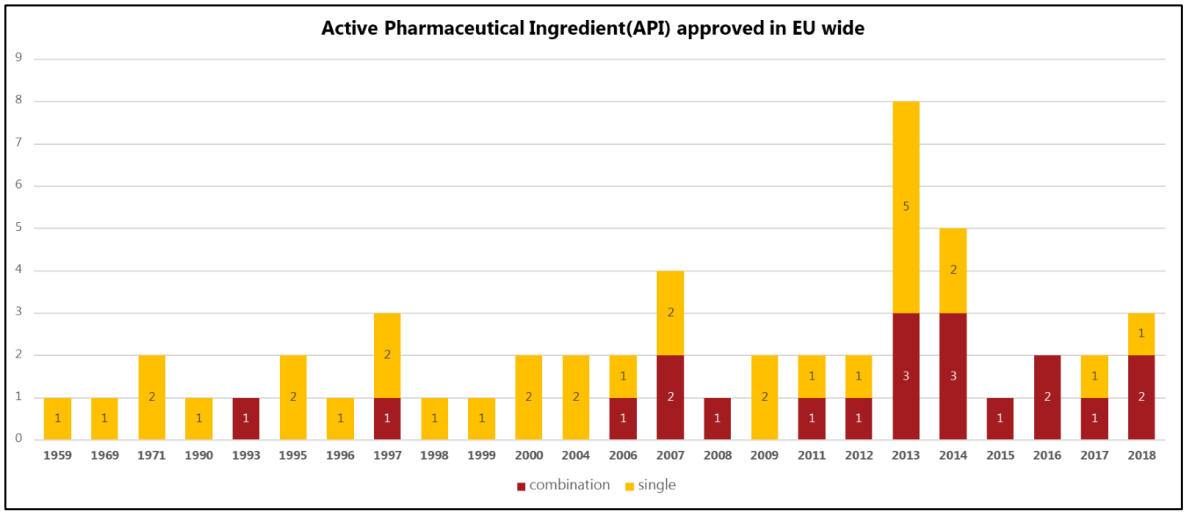
- Due to the current discrepancies between metformin-containing medicinal products in Europe, a wider review of the risk of lactic acidosis and on its use in renally impaired patients should be considered.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

Post-meeting note: the Dutch Medicines Agency (MEB) sent a letter of notification dated 25/01/2016 of a referral under Article 31 of Directive 2001/83/EC to the CHMP for the review of metformin-containing medicinal products with respect to the risk of lactic acidosis and use in patients with renal failure (EMA/50029/2016).

[20] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Figure S2 Active Pharmaceutical Ingredient (API) approved in EU



54 APIs and combinations of APIs were approved in EU, with 23 were approved from 2012 to 2022. Authorisation date extracted from the 'List of Union Reference Dates and Frequency of Submission of Periodic Safety Update Reports' (EURD List). Tolbutamide and fixed combination of glipizide, metformin are not showed since their authorisation dates were missed in the EURD list.

Figure S3 All drug-AE evaluations included in the study. The X-axis represents the study period, while the Y-axis lists the drug–AE pairs. Colours indicate PRAC procedures and activities. Each drug–AE pair could have at least one evaluation. One drug-AE evaluation could involve at least one procedure or activity. For each drug–AE pair, blank spaces separate distinct evaluations.

Figure S3-1_ 1st generation antidiabetics: All post-marketing drug-AE evaluations related to 1st generation antidiabetics collected from PRAC meeting minutes (2012-2022).

Figure S3-2_DPP-4: All post-marketing drug-AE evaluations related to DPP-4is collected from PRAC meeting minutes (2012-2022).

Figure S3-3_GLP-1: All post-marketing drug-AE evaluations related to GLP-1RAs including fixed combination with insulin collected from PRAC meeting minutes (2012-2022).

Figure S3-4_SGLT-2: All post-marketing drug-AE evaluations related to SGLT-2 collected from PRAC meeting minutes (2012-2022).

Figure S3-5_Only 1 evaluation excludes PSURs: All post-marketing antidiabetic drug–AE pairs that were evaluated only once, excluding PSURs, were collected from PRAC meeting minutes (2012-2022).

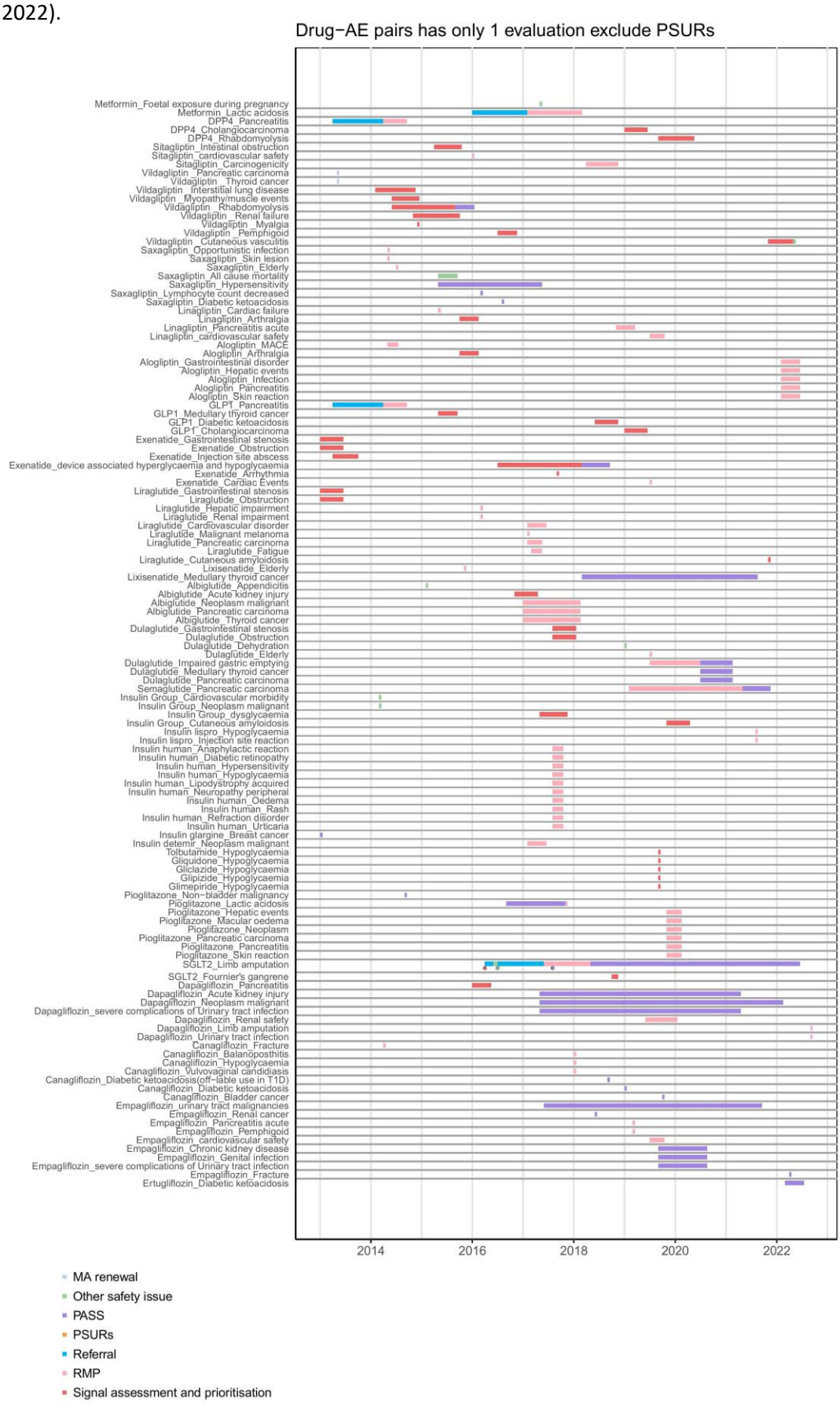


Figure S3-6_Only 1 evaluation only PSURs: All post-marketing antidiabetic drug–AE pairs that were evaluated only once, excluding non-PSURs, were collected from PRAC meeting minutes (2012-2022).

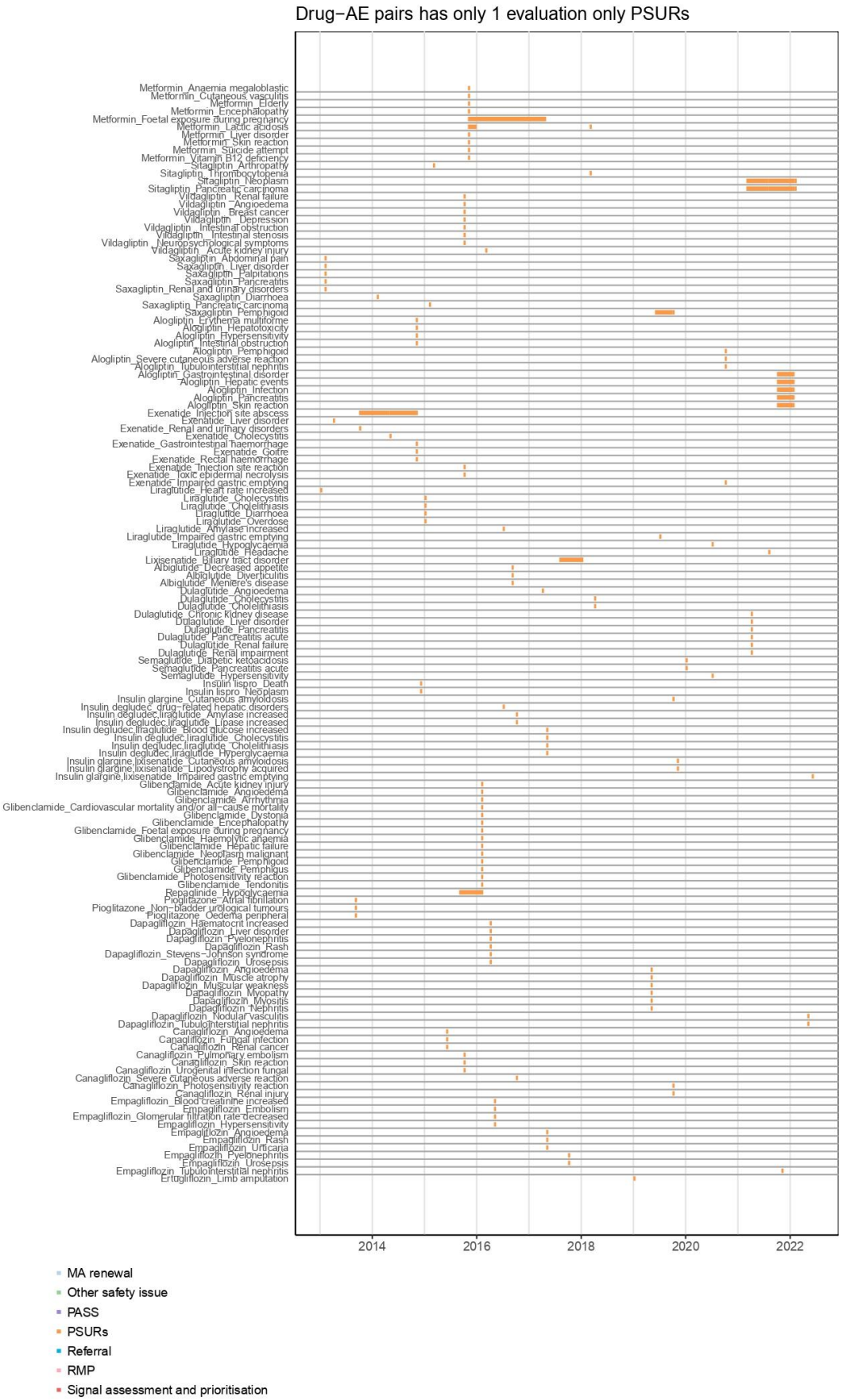


Figure S3-7_2 evaluations: All post-marketing antidiabetic drug–AE pairs that were evaluated twice were collected from PRAC meeting minutes (2012-2022).

Figure S3-8_More than 2 evaluations: All post-marketing antidiabetic drug–AE pairs that were evaluated more than twice collected from PRAC meeting minutes (2012-2022).

List S1: List of acronyms

Abbreviation	Full
aRMMs	Additional risk minimisation measures
CHMP	Committee for Medicinal Products for Human Use
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
EU	European Union
MA	Marketing authorisation
MA renewal	Renewals of the marketing authorisation, conditional renewal and annual reassessments
MAH	Marketing authorisation holder
Other safety issues	Other safety issues for discussion requested by the CHMP, EMA, or the Member States
PASS	Post-Authorization Safety Studies
PRAC	Pharmacovigilance Risk Assessment Committee
PSURs	Periodic Safety Update Reports
PV	Pharmacovigilance
Referrals	EU referral procedures for safety reasons
RMMs	Risk minimisation measures
RMP	Risk Management Plan
Signal Procedure	Signal assessment and prioritisation
SmPC	Summary of Product Characteristics