

Supplement

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Introduction to SSA and TreeScan

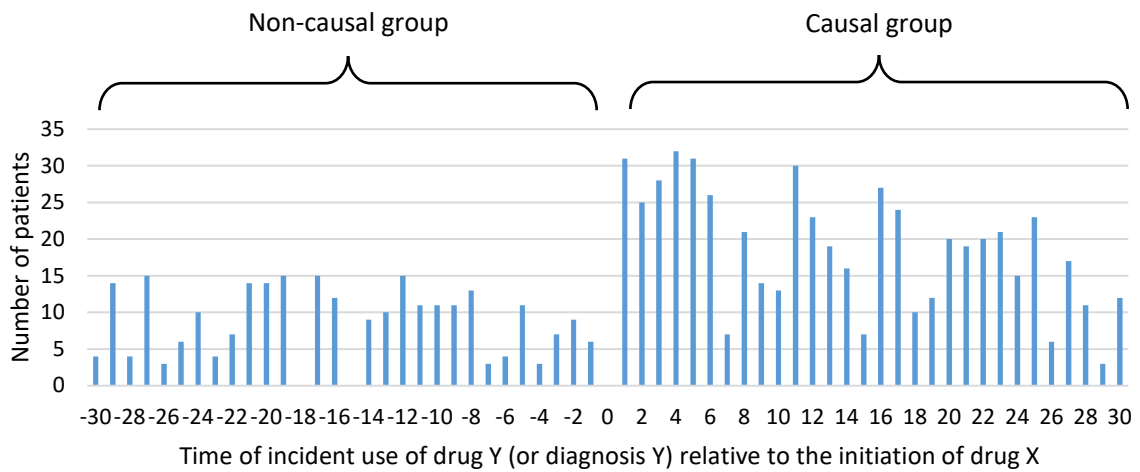
Sequence symmetry analysis (SSA)

This study utilized prescription SSA. Prescription SSA (PSSA) assumes that if an ADR caused by an index drug can be treated, or the symptoms of the ADR could be relieved by a marker drug, then an imbalanced higher frequency would be found in the prescription sequence of index drug followed by marker drug, compared to the inverse sequence. Within a pre-specified screening time interval relative to the first prescription date of the index drug for a given population, the number of prescriptions with suspected causal sequence divided by the number of prescriptions with the inverse sequence yields the sequence ratio (SR) (See **Supplement, Fig. 1**). An SR greater than 1 implies that prescription of the index drug followed by prescription of the marker drug occurs more frequently than the other way around. In other words, an SR greater than one indicates that use of the index drug is associated with increased prescription of the marker drug, implying that the latter might be being used to treat potential AEs caused by the index drug. To further adjust for potential bias caused by the secular trend in drug prescription rate, a null-effect SR following Tsiropoulos' method [1] is used to generate an adjusted SR. The 95% confidence interval (CI) for the adjusted SR is derived using a normal approximation to the binomial distribution [2]. Details of the PSSA methodology are described in Hallas' [3] and Lai's [4] papers.

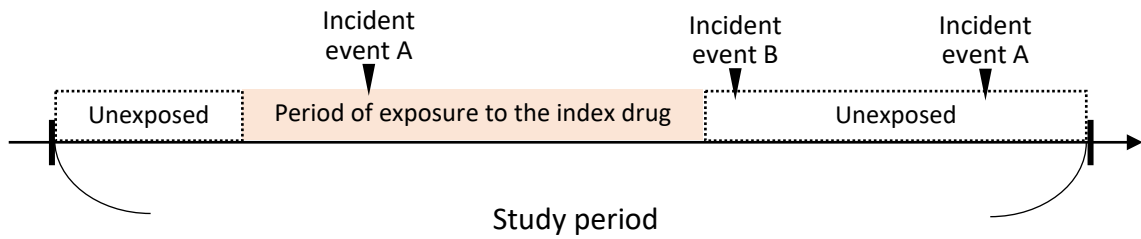
Tree-based scan statistics (TreeScan)

The 'tree' in TreeScan refers to the data hierarchy to be mined or scanned. If one's aim is to mine the data for potential ADRs to a pre-specified index drug, then the tree can be understood as a diagnostic tree encoded by a specific coding system in a hierarchical manner. Each node on the tree represents a different group of events. After defining the diagnostic tree to be scanned, the TreeScan model calculates the likelihood for each node as well as nodes coded at a broader- and at a more granular level on the tree, under both the null and alternative hypotheses, whereby at least one node of the event occurs more frequently than in the rest of the tree. For instance, if the analysed event was coded as E11.1 in the ICD10-CM system, then in TreeScan a broader level of event coded as E11 and a more granular level of events coded as E11.10 and as E11.11 will be tested separately as well. The node with the maximum log likelihood ratio (LLR) is the most likely cluster of AEs. Following the Monte Carlo simulation, the distribution of test statistics under the null hypothesis is generated and the maximum LLR from the real dataset is ranked in the null distribution to obtain the p-value. Any event with a p-value less than a pre-specified significance level or a lower bound of 95% CI greater than 1 is considered as a significant alert. More information regarding methodology and statistics of TreeScan can be found in Kulldoff's [5] and Wang's [6] papers.

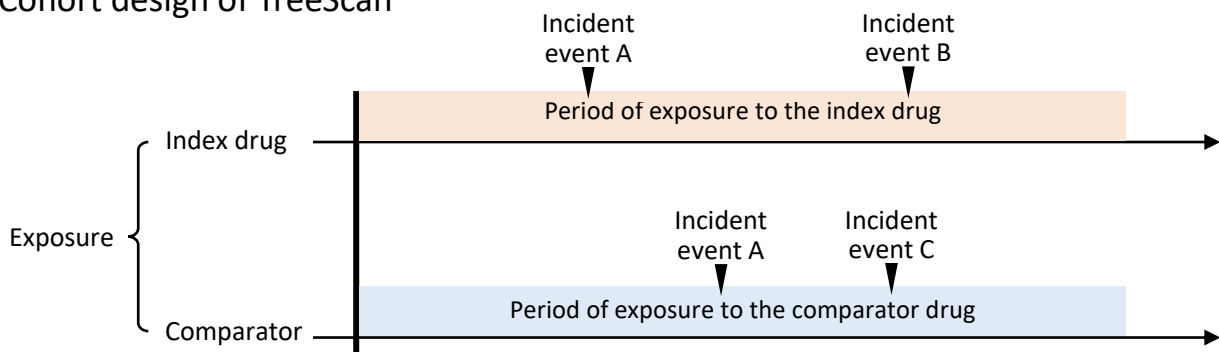
Sequence symmetry analysis



Self-controlled design of TreeScan



Cohort design of TreeScan



Supplementary Fig. 1: Sequence symmetry analysis and TreeScan designs

Supplementary Table 1. Characteristics of SGLT2 inhibitor and DPP4 inhibitor new users

	Before PS-matching				After PS-matching			
	SGLT2 inhibitor		DPP4 inhibitor		SGLT2 inhibitor		DPP4 inhibitor	
	N	%	N	%	N	%	N	%
No. of patients	138,611	-	346,428	-	118,308	-	118,308	-
Age, mean (\pm SD)	58.15	\pm 12.12	62.73	\pm 13.76	58.91	\pm 12.01	58.81	\pm 12.91
Male	76,233	55.00	188,074	54.29	64,676	54.67	64,398	54.43
Frequency of outpatient visits per year								
\leq 26	12,676	9.15	55,570	16.04	12,169	10.29	12,227	10.33
27-52	29,859	21.54	70,914	20.47	26,034	22.01	26,343	22.27
53-78	28,891	20.84	60,960	17.60	24,315	20.55	24,169	20.43
\geq 79	66,935	48.29	154,412	44.57	55,547	46.95	55,382	46.81
Admission of inpatient/ER	26,940	19.44	118,649	34.25	24,857	21.01	24,221	20.47
CCI, mean (\pm SD)	2.61	\pm 1.65	2.86	\pm 2.09	2.61	\pm 1.68	3.00	\pm 1.71
Comorbidity								
Hypertension	87,158	62.88	215,639	62.25	74,224	62.74	74,029	62.57
Dyslipidaemia	91,022	65.67	179,685	51.87	75,839	64.10	76,645	64.78
a								
CAD	26,973	19.46	58,535	16.90	22,266	18.82	22,210	18.77
PAD	2,645	1.91	7,778	2.25	2,268	1.92	2,287	1.93
Heart failure	6,075	4.38	20,333	5.87	5,303	4.48	5,259	4.45
Ischemic stroke	4,391	3.17	21,343	6.16	4,106	3.47	3,933	3.32
Retinopathy	14,614	10.54	25,416	7.34	11,509	9.73	11,483	9.71
Nephropathy	12,329	8.89	24,073	6.95	9,889	8.36	9,978	8.43
Neuropathy	26,301	18.97	53,314	15.39	21,002	17.75	20,721	17.51
Liver cirrhosis	1,323	0.95	6,336	1.83	1,231	1.04	1,178	1.00
Cancer	13,115	9.46	41,632	12.02	11,532	9.75	11,527	9.74
Co-medication (baseline)								
Anti-platelet	47,718	34.43	115,344	33.30	40,077	33.88	39,981	33.79
Beta-blocker	47,950	34.59	113,201	32.68	40,270	34.04	39,882	33.71
ACEI/ARB	84,305	60.82	184,006	53.12	70,208	59.34	69,962	59.14
CCB	40,716	29.37	131,158	37.86	36,480	30.83	36,342	30.72
Diuretic	21,442	15.47	75,866	21.90	19,028	16.08	18,725	15.83
Statin	96,291	69.47	177,393	51.21	78,925	66.71	79,449	67.15
Fibrate	18,159	13.10	34,591	9.99	14,913	12.61	14,924	12.61
Metformin	110,662	79.84	227,062	65.54	91,551	77.38	91,515	77.35
Sulfonylurea	71,825	51.82	148,933	42.99	60,243	50.92	60,610	51.23
Glinide	8,840	6.38	27,700	8.00	7,597	6.42	7,524	6.36
Acarbose	29,200	21.07	40,806	11.78	21,748	18.38	21,720	18.36
TZD	30,425	21.95	39,415	11.38	21,859	18.48	21,751	18.39
GLP-1RA	2,556	1.84	1,194	0.34	1,213	1.03	1,031	0.87
Insulin	38,215	27.57	90,000	25.98	29,506	24.94	28,507	24.10
Concomitant OAD (index date)								
Metformin	86,648	62.51	104,433	30.15	67,585	57.13	67,672	57.20
Sulfonylurea	48,941	35.31	91,164	26.32	40,439	34.18	40,187	33.97
Glinide	4,347	3.14	15,017	4.33	3,795	3.21	3,758	3.18
Acarbose	16,840	12.15	20,025	5.78	12,085	10.21	11,858	10.02
TZD	19,242	13.88	14,000	4.04	11,456	9.68	10,790	9.12
GLP-1RA	291	0.21	75	0.02	100	0.08	70	0.06

Insulin	25,552	18.43	36,625	10.57	18,072	15.28	17,418	14.72
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Abbreviations: CCI=Charlson Comorbidity Index; ER=emergency room; PS=propensity score.

Supplementary Table 2. Detected alerts of NFQs: Results from prescription sequence symmetry analysis

Clinical classification*	Type	Marker drug	Name	Crude SR	Adjusted SR	95% CI	Pair No	FQ SSA	Corresponding findings in TreeScan
Gastrointestinal Anaemia	AD R	A02BC06	Dexlansoprazole	1.27	1.21	(1.04 - 1.41)	24941		Dyspepsia and other specified disorders of stomach function
	AD R	B03AB04	Ferric hydroxide	1.26	1.25	(1.01 - 1.54)	19760		
Lipid	AD R	B03AE01	Iron, vitamin B12 and folic acid	1.66	1.65	(1.12 - 2.43)	5478	V	
	AD R	C10AA01	Simvastatin	1.69	1.79	(1.24 - 2.59)	13785	V	
Nervous system	AD R	N03AX16	Pregabalin	1.53	1.44	(1.07 - 1.94)	11536	V	Neuralgia, neuritis and radiculitis
Anti-inflammation	AD R	M01AG04	Meclofenamic acid	1.48	1.44	(1.06 - 1.97)	11266		Lumbago, backache, sprains and strains of other parts of the back
Psychiatric	AD R	N06AA02	Imipramine	1.34	1.35	(1.22 - 1.50)	70661	V	
	AD R	N06AA09	Amitriptyline	1.37	1.37	(1.00 - 1.87)	12786		
	AD R	N06AX11	Mirtazapine	1.39	1.37	(1.08 - 1.73)	15890	V	
Eye	AD Rr	S01HA02	Oxybuprocaine	1.27	1.28	(1.01 - 1.64)	17368		Inflammation of eyelids, foreign body on external eye
Urinary tract	lr	A12BA02	Potassium citrate	1.39	1.38	(1.04 - 1.84)	6815	V	Calculus of kidney, ureter, lower urinary tract
	lr	G04BD04	Oxybutynin	1.31	1.34	(1.23 - 1.46)	118349		Neurogenic bladder, other
	lr	G04BD06	Propiverine	1.68	1.69	(1.29 - 2.23)	9143	V	functional disorder of the bladder
	lr	G04BD07	Tolterodine	1.63	1.63	(1.43 - 1.87)	40911	V	
	lr	G04BD08	Solifenacin	2.14	2.12	(1.79 - 2.51)	29423	V	
	lr	G04BD12	Mirabegron	2.36	2.25	(1.81 - 2.79)	11363	V	
	lr	H01BA02	Desmopressin	1.63	1.64	(1.31 - 2.07)	12528	V	
Genital tract	lr	D01BA02	Terbinafine	1.26	1.22	(1.00 - 1.48)	16170		Candidiasis
	lr	G01AF07	Isoconazole	1.30	1.26	(1.01 - 1.57)	18671		
	lr	G01AF12	Fenticonazole	1.75	1.56	(1.26 - 1.93)	14975	V	
Respiratory	lr	J02AC01	Fluconazole	1.48	1.44	(1.20 - 1.74)	18046	V	
	lr	R06AA08	Carbinoxamine	1.81	1.56	(1.07 - 2.27)	7343		
	lr	R06AA57	Diphenylpyraline, combinations	1.28	1.51	(1.02 - 2.25)	6926		
	CH	B05XA05	Magnesium sulfate	1.36	1.31	(1.00 - 1.70)	9785		Complications of pregnancy

Pregnancy/ menstrual cycle	CH	G03DA04	Progesterone	1.19	1.22	(1.08 - 1.37)	59999	V	Abortion, conditions associated with menstrual cycle, menopausal and other perimenopausal disorders
Medications used in critical care / fluids	CH	A06AD11	Lactulose	1.23	1.20	(1.05 - 1.38)	33641	V	
	CH	A06AD17	Sodium phosphate	1.23	1.23	(1.10 - 1.38)	56549		
	CH	A03AB02	Glycopyrronium bromide	1.74	1.68	(1.08 - 2.62)	4149		
	CH	A03BA01	Atropine	1.61	1.63	(1.27 - 2.08)	11448	V	
	CH	B01AB01	Heparin	1.27	1.26	(1.08 - 1.48)	29677		
	CH	B03XA02	Darbepoetin alfa	1.74	1.78	(1.01 - 3.13)	3058	V	
	CH	B05BA01	Amino acids	1.39	1.33	(1.07 - 1.65)	12071		
	CH	B05BA10	Combinations	1.51	1.54	(1.13 - 2.11)	6984		
	CH	B05CB01	Sodium chloride	1.45	1.41	(1.18 - 1.69)	18536	V	
	CH	C01BB01	Lidocaine	1.42	1.38	(1.19 - 1.60)	34670		
	CH	C01CA03	Norepinephrine	1.38	1.31	(1.07 - 1.61)	13274	V	
	CH	C01CA04	Dopamine	1.85	1.83	(1.44 - 2.33)	12016	V	
	CH	C01CA24	Epinephrine	1.59	1.60	(1.39 - 1.84)	37290	V	
	CH	H01BA06	Argipressin	1.55	1.53	(1.03 - 2.27)	4600	V	
Broad- spectrum antibiotics	CH	N01AX10	Propofol	1.24	1.23	(1.06 - 1.43)	23058		
	CH	N07AA01	Neostigmine	1.36	1.38	(1.10 - 1.73)	14068		
	CH	J01AA12	Tigecycline	2.24	2.18	(1.23 - 3.86)	2000	V	
	CH	J01CR04	Sultamicillin	1.52	1.43	(1.20 - 1.71)	19026		
	CH	J01DD01	Cefotaxime	1.97	1.83	(1.18 - 2.85)	3417		
	CH	J01DD02	Ceftazidime	1.32	1.31	(1.09 - 1.56)	17086	V	
	CH	J01DD08	Cefixime	1.54	1.45	(1.26 - 1.68)	32316	V	
	CH	J01DD14	Ceftibuten	1.31	1.27	(1.11 - 1.45)	33260	V	
	CH	J01DE01	Cefepime	1.61	1.54	(1.19 - 2.00)	8227	V	
	CH	J01DH02	Meropenem	1.78	1.67	(1.23 - 2.27)	6910	V	
	CH	J01DH03	Ertapenem	1.33	1.31	(1.07 - 1.61)	13595	V	
	CH	J01DH51	Imipenem and enzyme inhibitor	1.51	1.44	(1.07 - 1.95)	6031	V	
	CH	J01MA02	Ciprofloxacin	1.19	1.20	(1.11 - 1.30)	102764		
	CH	J01XA02	Teicoplanin	1.60	1.54	(1.13 - 2.08)	7344	V	
Cancer- related	CH	J01XB01	Colistin	1.82	1.66	(1.05 - 2.64)	2489	V	
	CH	J01XX08	Linezolid	2.71	2.50	(1.05 - 5.95)	1048	V	
	CH	J04AK01	Pyrazinamide	2.89	2.94	(1.38 - 6.28)	1293	V	
	CH	J04AK02	Ethambutol	3.50	3.56	(1.76 - 7.19)	2316	V	
	CH	J04AM02	Rifampicin and isoniazid	3.11	3.15	(1.48 - 6.67)	2249	V	
	CH	A04AA02	Granisetron	2.16	2.19	(1.48 - 3.23)	4128		Malignant neoplasm of breast, bladder, kidney and other unspecified urinary organs, genitourinary system
	CH	A04AA05	Palonosetron	3.21	3.16	(2.20 - 4.55)	5511		
	CH	A04AD12	Aprepitant	3.04	3.12	(1.97 - 4.95)	3801		
	CH	L01BC02	Fluorouracil	3.00	3.08	(1.94 - 4.90)	3945		
	CH	L01BC05	Gemcitabine	3.07	3.06	(1.71 - 5.49)	1697		

CH	L01BC06	Capecitabine	2.20	2.19	(1.03 - 4.61)	1460	V
CH	L01DB01	Doxorubicin	2.29	2.18	(1.16 - 4.09)	2537	
CH	L01DB03	Epirubicin	2.05	2.04	(1.21 - 3.43)	2706	
CH	L01DC03	Mitomycin	2.42	2.24	(1.42 - 3.53)	2930	
CH	L01XA01	Cisplatin	3.41	3.48	(2.35 - 5.16)	4493	
CH	L01XA02	Carboplatin	2.88	2.83	(1.63 - 4.91)	1633	
CH	L02AB01	Megestrol	1.82	1.74	(1.29 - 2.34)	6735	
CH	L02AE02	Leuprorelin	5.21	5.28	(3.23 - 8.62)	2342	V
CH	L02AE03	Goserelin	3.00	3.14	(1.14 - 8.63)	806	V
CH	L02BB03	Bicalutamide	7.78	8.00	(4.00 - 16.0)	2107	V
CH	L03AX03	BCG vaccine	3.17	2.93	(1.17 - 7.33)	591	
CH	L03AA02	Filgrastim	1.83	1.81	(1.09 - 3.01)	2538	
CH	L03AA10	Lenograstim	2.43	2.42	(1.00 - 5.83)	1331	
CH	M05BA03	Pamidronic acid	5.00	5.23	(1.15 - 23.9)	416	V
CH	M05BA08	Zoledronic acid	1.74	1.78	(1.07 - 2.98)	3124	V
CH	N02AA03	Hydromorphone	3.20	3.03	(1.11 - 8.28)	646	
CH	N02AA05	Oxycodone	3.89	2.38	(1.14 - 4.95)	1571	
CH	N02AB03	Fentanyl	3.65	3.49	(2.20 - 5.54)	4476	V
CH	V03AF03	Calcium folinate	2.16	2.06	(1.28 - 3.31)	3438	V

*Clinical classification was expressed in either disease or medication system.

Abbreviation: ADR=known adverse drug reaction; ADRr=events related to known adverse drug reaction; CH=cohort-related; I=indication; Ir=indication-related; PT=protopathic bias; S=signal.

Supplementary Table 3. Detected alerts of NFQs: Results from propensity score-matched TreeScan

Clinical classification*	Type	Node†	Tree level	ICD 9 Diagnosis	Observations	Cases	Expected	RR	LLR	P-value
Infections	I	0085	2	Bacterial enteritis, unspecified	1221	729	610.5	1.19	23.15	0.0001
	I	0093	2	Diarrhoea of presumed infectious origin	3935	2105	1967.5	1.07	9.62	0.0446
	I	098	1	Gonococcal infections	548	334	274	1.22	13.25	0.0011
	I	099	1	Other venereal diseases	1239	916	619.5	1.48	147.89	0.0001
	Ir	112	1	Candidiasis	22970	12950	11485	1.13	187.38	0.0001
	Ir	122	1	Echinococcosis	38	35	19	1.84	15.84	0.0003
	Ir	131	1	Trichomoniasis	2613	1757	1306.5	1.34	158.57	0.0001
	I	0994	2	Other nongonococcal urethritis [NGU]	838	678	419	1.62	172.27	0.0001
	Ir	1121	2	Candidiasis of vulva and vagina	17277	10519	8638.5	1.22	412.66	0.0001
	Ir	1221	2	Echinococcus granulosus infection of lung	38	35	19	1.84	15.84	0.0003
	Ir	1310	2	Urogenital trichomoniasis	2539	1714	1269.5	1.35	158.98	0.0001
	Ir	1341	2	Other arthropod infestation	93	69	46.5	1.48	11.36	0.0061
	I	09940	3	Other unspecified nongonococcal urethritis	732	618	366	1.69	190.77	0.0001
	Ir	13100	3	Urogenital trichomoniasis, unspecified	571	373	285.5	1.31	27.25	0.0001
Ir	13101	3	Trichomonal vulvovaginitis	1927	1321	963.5	1.37	135.87	0.0001	
Neoplasms	PT	188	1	Malignant neoplasm of bladder	2440	1678	1220	1.38	176.22	0.0001
	PT	189	1	Malignant neoplasm of kidney and other unspecified urinary organs	1424	861	712	1.21	31.41	0.0001
	PT	218	1	Uterine leiomyoma	11674	6498	5837	1.11	75.01	0.0001
	PT	219	1	Other benign neoplasm of uterus	2413	1322	1206.5	1.1	11.07	0.01
	PT	220	1	Benign neoplasm of ovary	6035	3372	3017.5	1.12	41.74	0.0001
	PT	223	1	Benign neoplasm of kidney and other urinary organs	903	568	451.5	1.26	30.40	0.0001
	PT	233	1	Carcinoma in situ of breast and genitourinary system	637	376	318.5	1.18	10.44	0.0172
	PT	1882	2	Malignant neoplasm of lateral wall of urinary bladder	342	249	171	1.46	36.93	0.0001
	PT	1884	2	Malignant neoplasm of posterior wall of urinary bladder	87	70	43.5	1.61	17.33	0.0001
	PT	1889	2	Malignant neoplasm of bladder, part unspecified	1403	971	701.5	1.38	106.25	0.0001
	PT	1891	2	Malignant neoplasm of renal pelvis	411	265	205.5	1.29	17.48	0.0001
	PT	1892	2	Malignant neoplasm of ureter	346	228	173	1.32	17.79	0.0001
	PT	2189	2	Leiomyoma of uterus, unspecified	9045	5091	4522.5	1.13	71.65	0.0001
	PT	2219	2	Benign neoplasm of female genital organ, site unspecified	153	104	76.5	1.36	10.11	0.0252
	PT	2233	2	Benign neoplasm of bladder	151	117	75.5	1.55	24.13	0.0001
	PT	2239	2	Benign neoplasm of urinary organs, site unspecified	88	65	44	1.48	10.44	0.0169

Eye disorders	PT	2298	2	Benign neoplasm of other specified sites	513	311	256.5	1.21	11.67	0.0047	
	PT	2394	2	Neoplasm of unspecified nature of bladder	315	218	157.5	1.38	23.85	0.0001	
	PT	6117	2	Signs and symptoms in breast	3320	1823	1660	1.1	16.03	0.0003	
	ADR	368	1	Visual disturbances	16124	8428	8062	1.05	16.62	0.0001	
	ADRr	370	1	Keratitis	19086	9892	9543	1.04	12.77	0.0019	
	ADRr	372	1	Disorders of conjunctiva	114719	59233	57359.5	1.03	61.20	0.0001	
	ADRr	373	1	Inflammation of eyelids	25175	13492	12587.5	1.07	65.05	0.0001	
	ADRr	930	1	Foreign body on external eye	13350	7159	6675	1.07	35.13	0.0001	
	ADR	3681	2	Subjective visual disturbances	15499	8128	7749.5	1.05	18.49	0.0001	
	ADRr	3702	2	Superficial keratitis without conjunctivitis	12012	6279	6006	1.05	12.41	0.0028	
	ADRr	3721	2	Chronic conjunctivitis	52817	27432	26408.5	1.04	39.68	0.0001	
	ADRr	3725	2	Conjunctival degenerations and deposits	5653	3000	2826.5	1.06	10.66	0.0133	
	ADRr	3730	2	Blepharitis	5620	2984	2810	1.06	10.78	0.0122	
	ADRr	3731	2	Hordeolum and other deep inflammation of eyelid	16073	8668	8036.5	1.08	49.67	0.0001	
Nervous System	ADRr	9301	2	Foreign body in conjunctival sac	8768	4729	4384	1.08	27.18	0.0001	
	ADRr	36813	3	Visual discomfort	15281	8008	7640.5	1.05	17.68	0.0001	
	ADRr	37021	3	Punctate keratitis	7671	4058	3835.5	1.06	12.91	0.0015	
	ADRr	37210	3	Chronic conjunctivitis, unspecified	24643	12899	12321.5	1.05	27.08	0.0001	
	ADRr	37254	3	Conjunctival concretions	3569	1943	1784.5	1.09	14.10	0.0006	
	ADRr	37312	3	Hordeolum internum	8454	4657	4227	1.1	43.82	0.0001	
	ADRr	37991	3	Pain in or around eye	630	387	315	1.23	16.60	0.0001	
	ADRr	344	1	Other paralytic syndromes	2867	1639	1433.5	1.14	29.56	0.0001	
	ADRr	3446	2	Cauda equina syndrome	1416	1014	708	1.43	136.71	0.0001	
	ADR	3499	2	Unspecified disorders of nervous system	1413	801	706.5	1.13	12.68	0.0019	
	ADR	7292	2	Neuralgia, neuritis and radiculitis, unspecified	12932	6927	6466	1.07	32.90	0.0001	
	ADRr	34461	3	Cauda equina syndrome with neurogenic bladder	1297	948	648.5	1.46	143.71	0.0001	
	Ear disorders	Ir	384	1	Other disorders of tympanic membrane	1439	808	719.5	1.12	10.91	0.0114
		ADR	386	1	Vertiginous syndromes and other disorders of vestibular system	25716	13738	12858	1.07	60.27	0.0001
Ir		3809	2	Unspecified disorder of external ear	488	293	244	1.2	9.91	0.0294	
I		3814	2	Nonsuppurative otitis media, not specified as acute or chronic	1922	1067	961	1.11	11.72	0.0047	
I		3821	2	Chronic tubotympanic suppurative otitis media	495	407	247.5	1.64	111.44	0.0001	
ADRr		3860	2	Meniere's disease	4231	2483	2115.5	1.17	64.17	0.0001	
ADRr		3861	2	Other and unspecified peripheral vertigo	12876	6729	6438	1.05	13.16	0.0013	
ADRr		3869	2	Unspecified vertiginous syndromes and labyrinthine disorders	5637	2995	2818.5	1.06	11.06	0.0101	
ADR		3883	2	Tinnitus	10988	5791	5494	1.05	16.06	0.0003	
Ir		8726	2	Open wound to other specified parts of ear,	116	83	58	1.43	11.14	0.008	

			without mention of complication							
	Ir	38011	3	Acute infection of pinna	545	491	272.5	1.8	201.70	0.0001
	Ir	38013	3	Other acute infection of external ear	549	330	274.5	1.2	11.30	0.0063
	Ir	38015	3	Chronic mycotic otitis externa	3160	1704	1580	1.08	9.74	0.036
	I	38100	3	Acute nonsuppurative otitis media, unspecified	1477	832	738.5	1.13	11.87	0.0041
	ADRr	38600	3	Meniere's disease, unspecified	3809	2275	1904.5	1.19	72.54	0.0001
	ADRr	38612	3	Vestibular neuronitis	2049	1201	1024.5	1.17	30.56	0.0001
	ADR	38831	3	Subjective tinnitus	1153	826	576.5	1.43	111.63	0.0001
	Ir	87202	3	Open wound of auditory canal, without mention of complication	79	64	39.5	1.62	16.36	0.0003
	Ir	87261	3	Open wound of ear drum, without mention of complication	116	83	58	1.43	11.14	0.008
	ADRr	V721	2	Examination of ears and hearing	331	207	165.5	1.25	10.52	0.0157
Respiratory System	Ir	4610	2	Acute sinusitis of maxillary	7544	4365	3772	1.16	93.61	0.0001
	I	4618	2	Other acute sinusitis	9047	4780	4523.5	1.06	14.55	0.0004
	Ir	4642	2	Acute laryngotracheitis	13675	7678	6837.5	1.12	103.58	0.0001
	Ir	4732	2	Chronic sinusitis of ethmoidal	236	153	118	1.3	10.54	0.0147
	Ir	4760	2	Chronic laryngitis	888	511	444	1.15	10.15	0.0239
	Ir	4770	2	Allergic rhinitis due to pollen	1334	932	667	1.4	108.25	0.0001
	Ir	46420	3	Acute laryngotracheitis without mention of obstruction	13263	7468	6631.5	1.13	105.80	0.0001
	Ir	46611	3	Acute bronchiolitis due to respiratory syncytial virus (RSV)	4509	3056	2254.5	1.36	291.27	0.0001
Skin disorders	ADR	698	1	Pruritus and related conditions	50119	26590	25059.5	1.06	93.53	0.0001
	ADRr	6962	2	Parapsoriasis	205	157	102.5	1.53	30.53	0.0001
Oral Cavity	Ir	523	1	Gingival and periodontal diseases	43803	22396	21901.5	1.02	11.17	0.0079
	Ir	5233	2	Acute periodontitis	14062	7311	7031	1.04	11.15	0.0079
	Ir	5296	2	Glossodynia	122	89	61	1.46	13.35	0.0011
Gastrointestinal System	ADR	535	1	Gastritis and duodenitis	86456	44325	43228	1.03	27.84	0.0001
	ADRr	536	1	Disorders of function of the stomach	62350	32265	31175	1.03	38.12	0.0001
	I	555	1	Regional enteritis	6338	3812	3169	1.2	131.38	0.0001
	Ir	558	1	Other non-infectious gastroenteritis and colitis	73235	38302	36617.5	1.05	77.52	0.0001
	ADR	564	1	Functional digestive disorders, not elsewhere classified	82488	42664	41244	1.03	48.90	0.0001
	ADRr	787	1	Symptoms involving digestive system	55518	28587	27759	1.03	24.70	0.0001
	ADRr	789	1	Other symptoms involving abdomen and pelvis	108872	60248	54436	1.11	621.72	0.0001
	ADR	5350	2	Acute gastritis	43936	22500	21968	1.02	12.88	0.0016
	ADR	5355	2	Unspecified gastritis and gastroduodenitis	30924	16268	15462	1.05	42.03	0.0001
	ADR	5368	2	Dyspepsia and other specified disorders of function of stomach	25107	13199	12553.5	1.05	33.21	0.0001

Genitourinary System	ADDr	5369	2	Unspecified functional disorder of stomach	36117	18497	18058.5	1.02	10.65	0.0137
	ADDr	5509	2	Inguinal hernia, without mention of obstruction or gangrene	1686	940	843	1.12	11.19	0.0071
	I	5550	2	Regional enteritis, small intestine	1362	943	681	1.38	103.45	0.0001
	I	5559	2	Regional enteritis, unspecified site	3316	1952	1658	1.18	52.41	0.0001
	Ir	5589	2	Other and unspecified non-infectious gastroenteritis and colitis	72120	37804	36060	1.05	84.38	0.0001
	ADR	5645	2	Functional diarrhoea	3921	2102	1960.5	1.07	10.22	0.0229
	ADDr	5649	2	Unspecified functional disorder of intestine	23471	13104	11735.5	1.12	159.95	0.0001
	ADR	7873	2	Flatulence, eructation, and gas pain	22247	11994	11123.5	1.08	68.19	0.0001
	Ir	7890	2	Abdominal pain	104618	58152	52309	1.11	654.04	0.0001
	Ir	7899	2	Other symptoms involving abdomen and pelvis	1081	851	540.5	1.57	189.77	0.0001
	ADR	53500	3	Acute gastritis, without mention of haemorrhage	42723	21898	21361.5	1.03	13.48	0.0009
	ADR	53550	3	Unspecified gastritis and gastroduodenitis, without mention of haemorrhage	29996	15782	14998	1.05	41.00	0.0001
	ADDr	55090	3	Inguinal hernia, without mention of obstruction or gangrene, unilateral or unspecified (not specified as recurrent)	1357	781	678.5	1.15	15.54	0.0003
	ADDr	78799	3	Other symptoms involving digestive system	1545	948	772.5	1.23	40.22	0.0001
	Ir	78900	3	Abdominal pain, unspecified site	65982	37408	32991	1.13	593.15	0.0001
	Ir	78904	3	Abdominal pain, left lower quadrant	2329	1346	1164.5	1.16	28.40	0.0001
	Ir	78905	3	Abdominal pain, periumbilical	2248	1235	1124	1.1	10.98	0.0108
	Ir	78907	3	Abdominal pain, generalized	2015	1249	1007.5	1.24	58.46	0.0001
	Ir	78909	3	Abdominal pain, other specified site	11020	5970	5510	1.08	38.45	0.0001
	Ir	591	1	Hydronephrosis	16783	10728	8391.5	1.28	659.25	0.0001
	Ir	592	1	Calculus of kidney and ureter	51814	35052	25907	1.35	3298.75	0.0001
	Ir	594	1	Calculus of lower urinary tract	3089	2155	1544.5	1.4	248.03	0.0001
	I	595	1	Cystitis	123955	89321	61977.5	1.44	12488.96	0.0001
	Ir	596	1	Other disorders of bladder	16525	10772	8262.5	1.3	774.36	0.0001
	I	597	1	Urethritis, not sexually transmitted, and urethral syndrome	22032	14260	11016	1.29	969.61	0.0001
	Ir	598	1	Urethral stricture	1234	806	617	1.31	58.84	0.0001
	Ir	599	1	Other disorders of urethra and urinary tract	197264	120469	98632	1.22	4874.98	0.0001
	Ir	600	1	Hyperplasia of prostate	29423	16999	14711.5	1.16	357.13	0.0001
	I	601	1	Inflammatory diseases of prostate	15838	9168	7919	1.16	197.82	0.0001
	Ir	605	1	Redundant prepuce and phimosis	859	541	429.5	1.26	29.28	0.0001
	Ir	607	1	Disorders of penis	3825	2325	1912.5	1.22	89.67	0.0001
	Ir	614	1	Inflammatory disease of ovary, fallopian tube, pelvic cellular tissue and peritoneum	41848	24058	20924	1.15	471.18	0.0001
	Ir	615	1	Inflammatory diseases of uterus, except cervix	7632	4874	3816	1.28	297.21	0.0001

Ir	616	1	Inflammatory disease of cervix, vagina and vulva	108405	67147	54202.5	1.24	3121.45	0.0001
PT	617	1	Endometriosis	6745	3597	3372.5	1.07	14.96	0.0003
PT	618	1	Genital prolapse	2521	1523	1260.5	1.21	55.07	0.0001
PT	621	1	Disorders of uterus, not elsewhere classified	3749	2101	1874.5	1.12	27.44	0.0001
PT	622	1	Noninflammatory disorders of cervix	11522	6528	5761	1.13	102.42	0.0001
PT	623	1	Noninflammatory disorders of vagina	10738	6036	5369	1.12	83.08	0.0001
PT	625	1	Pain and other symptoms associated with female genital organs	15434	8810	7717	1.14	155.33	0.0001
PT	626	1	Disorders of menstruation and other abnormal bleeding from female genital tract	79850	44933	39925	1.13	629.84	0.0001
PT	627	1	Menopausal and postmenopausal disorders	17856	10458	8928	1.17	263.50	0.0001
PT	628	1	Infertility, female	3414	1898	1707	1.11	21.42	0.0001
PT	629	1	Other disorders of female genital organs	1393	875	696.5	1.26	46.26	0.0001
Ir	788	1	Symptoms involving urinary system	93881	61360	46940.5	1.31	4501.91	0.0001
PT	2568	2	Other ovarian dysfunction	258	166	129	1.29	10.76	0.0123
I	5900	2	Chronic pyelonephritis	1007	697	503.5	1.38	76.31	0.0001
Ir	5920	2	Calculus of kidney	19249	12716	9624.5	1.32	1010.85	0.0001
Ir	5921	2	Calculus of ureter	20917	14431	10458.5	1.38	1547.45	0.0001
Ir	5929	2	Urinary calculus, unspecified	11319	7752	5659.5	1.37	792.33	0.0001
Ir	5932	2	Cyst of kidney, acquired	1187	683	593.5	1.15	13.55	0.0009
Ir	5933	2	Stricture or kinking of ureter	1938	1324	969	1.37	133.13	0.0001
Ir	5940	2	Calculus in diverticulum of the bladder	162	131	81	1.62	33.20	0.0001
Ir	5941	2	Other calculus in bladder	2073	1445	1036.5	1.39	165.45	0.0001
Ir	5942	2	Calculus in urethra	620	435	310	1.4	51.87	0.0001
I	5950	2	Acute cystitis	80283	58182	40141.5	1.45	8405.53	0.0001
I	5951	2	Chronic interstitial cystitis	1441	948	720.5	1.32	73.08	0.0001
I	5958	2	Other specified types of cystitis	970	614	485	1.27	34.73	0.0001
I	5959	2	Cystitis, unspecified	38413	28167	19206.5	1.47	4347.02	0.0001
Ir	5960	2	Bladder neck obstruction	799	571	399.5	1.43	76.07	0.0001
Ir	5964	2	Atony of bladder	1132	690	566	1.22	27.39	0.0001
Ir	5965	2	Other functional disorders of the bladder	12215	8008	6107.5	1.31	601.32	0.0001
Ir	5968	2	Other specified disorders of the bladder	1226	792	613	1.29	53.04	0.0001
Ir	5969	2	Unspecified disorder of the bladder	770	488	385	1.27	27.89	0.0001
I	5970	2	Urethral abscess	1470	913	735	1.24	43.54	0.0001
I	5978	2	Other urethritis	20254	13154	10127	1.3	918.76	0.0001
Ir	5989	2	Urethral stricture, unspecified	1024	682	512	1.33	57.53	0.0001
I	5990	2	Urinary tract infection, site not specified	158462	94992	79231	1.2	3156.26	0.0001
Ir	5993	2	Urethral caruncle	152	110	76	1.45	15.76	0.0003
Ir	5997	2	Haematuria	31748	21294	15874	1.34	1888.35	0.0001
Ir	5999	2	Unspecified disorder of urethra and urinary tract	3727	2512	1863.5	1.35	230.47	0.0001
Ir	6000	2	Hypertrophy (benign) of prostate	21122	12447	10561	1.18	338.62	0.0001

Ir	6009	2	Hyperplasia of prostate, unspecified	6142	3503	3071	1.14	60.97	0.0001
I	6011	2	Chronic prostatitis	6020	3703	3010	1.23	160.99	0.0001
I	6013	2	Prostatocystitis	271	191	135.5	1.41	23.42	0.0001
I	6019	2	Prostatitis, unspecified	4418	2601	2209	1.18	69.93	0.0001
Ir	6071	2	Balanoposthitis	2277	1392	1138.5	1.22	56.92	0.0001
Ir	6078	2	Other specified disorder of penis	1089	654	544.5	1.2	22.17	0.0001
Ir	6145	2	Acute or unspecified pelvic peritonitis, female	3389	2059	1694.5	1.22	79.02	0.0001
Ir	6149	2	Unspecified inflammatory disease of female pelvic organs and tissues	24800	15164	12400	1.22	621.31	0.0001
Ir	6150	2	Acute inflammatory diseases of uterus, except cervix	1781	1267	890.5	1.42	164.30	0.0001
Ir	6159	2	Unspecified inflammatory disease of the uterus	5735	3550	2867.5	1.24	164.01	0.0001
Ir	6160	2	Cervicitis and endocervicitis	8645	5228	4322.5	1.21	191.10	0.0001
Ir	6161	2	Vaginitis and vulvovaginitis	53739	34329	26869.5	1.28	2098.36	0.0001
Ir	6165	2	Ulceration of vulva	2043	1220	1021.5	1.19	38.82	0.0001
Ir	6168	2	Other specified inflammatory diseases of cervix, vagina, and vulva	2037	1122	1018.5	1.1	10.54	0.0147
Ir	6169	2	Unspecified inflammatory disease of cervix, vagina, and vulva	39263	23950	19631.5	1.22	957.79	0.0001
PT	6179	2	Endometriosis, site unspecified	1545	865	772.5	1.12	11.10	0.0083
PT	6180	2	Prolapse of vaginal walls, without mention of uterine prolapse	790	465	395	1.18	12.47	0.0027
PT	6184	2	Uterovaginal prolapse, unspecified	429	277	214.5	1.29	18.48	0.0001
PT	6189	2	Unspecified genital prolapse	327	205	163.5	1.25	10.65	0.0137
PT	6202	2	Other and unspecified ovarian cyst	5750	3046	2875	1.06	10.18	0.0236
PT	6214	2	Hematometra	280	185	140	1.32	14.72	0.0003
PT	6220	2	Erosion and ectropion of cervix	7267	4052	3633.5	1.12	48.31	0.0001
PT	6221	2	Dysplasia of cervix (uteri)	2568	1531	1284	1.19	47.81	0.0001
PT	6225	2	Incompetence of cervix	44	39	22	1.77	14.92	0.0003
PT	6227	2	Mucous polyp of cervix	1305	757	652.5	1.16	16.81	0.0001
PT	6235	2	Leukorrhea, not specified as infective	10153	5669	5076.5	1.12	69.31	0.0001
PT	6239	2	Unspecified noninflammatory disorder of vagina	289	209	144.5	1.45	29.83	0.0001
PT	6250	2	Dyspareunia	257	169	128.5	1.32	12.98	0.0014
PT	6253	2	Dysmenorrhea	9159	4969	4579.5	1.09	33.17	0.0001
PT	6256	2	Stress incontinence, female	2922	1946	1461	1.33	164.10	0.0001
PT	6259	2	Unspecified symptom associated with female genital organs	698	446	349	1.28	27.32	0.0001
PT	6260	2	Absence of menstruation	13852	8370	6926	1.21	303.28	0.0001
PT	6264	2	Irregular menstrual cycle	22246	11923	11123	1.07	57.59	0.0001
PT	6266	2	Metrorrhagia	7004	3992	3502	1.14	68.79	0.0001

PT	6268	2	Other disorders of menstruation and other abnormal bleeding from female genital tract	12123	7130	6061.5	1.18	189.34	0.0001
PT	6269	2	Unspecified disorder of menstruation and other abnormal bleeding from female genital tract	14660	8235	7330	1.12	112.02	0.0001
PT	6271	2	Postmenopausal bleeding	1136	670	568	1.18	18.42	0.0001
PT	6272	2	Menopausal or female climacteric states	9765	5591	4882.5	1.15	103.17	0.0001
PT	6273	2	Postmenopausal atrophic vaginitis	3342	2051	1671	1.23	87.18	0.0001
PT	6274	2	States associated with artificial menopause	107	84	53.5	1.57	18.48	0.0001
PT	6279	2	Unspecified menopausal and postmenopausal disorder	2919	1752	1459.5	1.2	59.02	0.0001
PT	6289	2	Infertility, female, of unspecified origin	1581	891	790.5	1.13	12.81	0.0019
PT	6298	2	Other specified disorders of female genital organs	689	440	344.5	1.28	26.82	0.0001
PT	6299	2	Unspecified disorder of female genital organs	704	435	352	1.24	19.76	0.0001
Ir	6981	2	Pruritus of genital organs	14610	8816	7305	1.21	314.81	0.0001
Ir	7880	2	Renal colic	6605	4571	3302.5	1.38	499.98	0.0001
Ir	7881	2	Dysuria	12760	8492	6380	1.33	712.51	0.0001
Ir	7882	2	Retention of urine	10082	5786	5041	1.15	110.51	0.0001
Ir	7883	2	Incontinence of urine	16264	10881	8132	1.34	947.85	0.0001
Ir	7884	2	Frequency of urination and polyuria	44142	29057	22071	1.32	2249.72	0.0001
Ir	7886	2	Other abnormality of urination	1314	860	657	1.31	63.76	0.0001
Ir	7888	2	Extravasation of urine	518	458	259	1.77	173.33	0.0001
Ir	7889	2	Other symptoms involving urinary system	1609	910	804.5	1.13	13.87	0.0006
PT	7950	2	Nonspecific abnormal Papanicolaou smear of cervix	270	181	135	1.34	15.99	0.0003
I	59000	3	Chronic pyelonephritis without lesion of renal medullary necrosis	959	675	479.5	1.41	82.08	0.0001
Ir	59389	3	Other specified disorders of kidney and ureter	689	404	344.5	1.17	10.33	0.0215
I	59589	3	Other specified types of cystitis	722	470	361	1.3	33.43	0.0001
Ir	59651	3	Hypertonicity of bladder	2959	2106	1479.5	1.42	273.85	0.0001
Ir	59654	3	Neurogenic bladder NOS	5327	3373	2663.5	1.27	191.30	0.0001
Ir	59655	3	Detrusor sphincter dyssynergia	217	146	108.5	1.35	13.23	0.0011
Ir	59659	3	Other functional disorder of bladder	3367	2176	1683.5	1.29	146.21	0.0001
I	59780	3	Urethritis, unspecified	17044	11311	8522	1.33	929.79	0.0001
Ir	59781	3	Urethral syndrome NOS	805	489	402.5	1.21	18.74	0.0001
I	59789	3	Other urethritis	2278	1270	1139	1.12	15.10	0.0003
Ir	59983	3	Urethral instability	111	84	55.5	1.51	15.36	0.0003
Ir	59984	3	Other specified disorders of urethra	161	109	80.5	1.35	10.31	0.0217
Ir	60490	3	Orchitis and epididymitis, unspecified	4331	2325	2165.5	1.07	11.76	0.0047
Ir	60491	3	Orchitis and epididymitis in diseases	167	115	83.5	1.38	12.18	0.0033

			classified elsewhere							
	Ir	60784	3	Impotence of organic origin	923	562	461.5	1.22	22.06	0.0001
	Ir	61610	3	Vaginitis and vulvovaginitis, unspecified	43869	27401	21934.5	1.25	1376.82	0.0001
	Ir	61611	3	Vaginitis and vulvovaginitis in diseases classified elsewhere	9148	6598	4574	1.44	927.41	0.0001
	Ir	61650	3	Ulceration of vulva, unspecified	1868	1137	934	1.22	44.48	0.0001
	Ir	78820	3	Retention of urine, unspecified	7731	4376	3865.5	1.13	67.62	0.0001
	Ir	78821	3	Incomplete bladder emptying	1254	765	627	1.22	30.62	0.0001
	Ir	78829	3	Other specified retention of urine	752	459	376	1.22	18.47	0.0001
	Ir	78830	3	Urinary incontinence, unspecified	6917	4751	3458.5	1.37	494.95	0.0001
	Ir	78831	3	Urge incontinence	6919	4608	3459.5	1.33	388.62	0.0001
	Ir	78833	3	Mixed incontinence (male)(female)	737	513	368.5	1.39	58.21	0.0001
	Ir	78836	3	Nocturnal enuresis	358	241	179	1.35	21.93	0.0001
	Ir	78841	3	Urinary frequency	36766	24810	18383	1.35	2295.16	0.0001
	Ir	78843	3	Nocturia	5199	2928	2599.5	1.13	41.62	0.0001
	Ir	78861	3	Splitting of urinary stream	322	269	161	1.67	79.19	0.0001
	Ir	78869	3	Other abnormality of urination	573	351	286.5	1.23	14.65	0.0003
	Ir	V536	2	Fitting and adjustment of urinary devices	482	398	241	1.65	111.12	0.0001
	Ir	V556	2	Attention to other artificial opening of urinary tract	113	89	56.5	1.58	19.89	0.0001
Pregnancy and childbirth	CH	V723	2	Gynaecological examination	3162	2043	1581	1.29	137.00	0.0001
	CH	634	1	Abortion	1390	794	695	1.14	14.15	0.0006
	CH	640	1	Haemorrhage in early pregnancy	7891	4706	3945.5	1.19	147.51	0.0001
	CH	641	1	Antepartum haemorrhage, abruptio placentae, and placenta previa	736	488	368	1.33	39.86	0.0001
	CH	643	1	Excessive vomiting in pregnancy	4632	2724	2316	1.18	72.25	0.0001
	CH	644	1	Early or threatened labour	1518	1082	759	1.43	141.94	0.0001
	CH	646	1	Other complications of pregnancy, not elsewhere classified	1233	855	616.5	1.39	94.72	0.0001
	CH	648	1	Other current conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium	754	560	377	1.49	92.70	0.0001
	CH	650	1	Normal delivery	958	657	479	1.37	67.76	0.0001
	CH	651	1	Multiple gestation	197	169	98.5	1.72	56.01	0.0001
	CH	652	1	Malposition and malpresentation of foetus	445	343	222.5	1.54	68.90	0.0001
	CH	654	1	Abnormality of organs and soft tissues of pelvis	422	295	211	1.4	34.39	0.0001
	CH	655	1	Known or suspected foetal abnormality affecting management of mother	240	210	120	1.75	75.93	0.0001
	CH	656	1	Other foetal and placental problems affecting management of mother	302	215	151	1.42	28.00	0.0001
	CH	658	1	Other problems associated with amniotic cavity and membranes	201	132	100.5	1.31	10.04	0.0264

CH	661	1	Abnormality of forces of labour	152	128	76	1.68	39.06	0.0001
CH	662	1	Long labour	127	97	63.5	1.53	18.60	0.0001
CH	664	1	Trauma to perineum and vulva during delivery	96	70	48	1.46	10.47	0.0161
CH	669	1	Other complications of labour and delivery, not elsewhere classified	191	131	95.5	1.37	13.52	0.0009
CH	765	1	Disorders relating to short gestation and unspecified low birthweight	117	84	58.5	1.44	11.50	0.0055
CH	770	1	Other respiratory conditions of foetus and new-born	134	106	67	1.58	24.20	0.0001
CH	6349	2	Abortion, without mention of complication	756	454	378	1.2	15.39	0.0003
CH	6400	2	Threatened abortion	6475	3902	3237.5	1.21	137.36	0.0001
CH	6410	2	Placenta previa without haemorrhage	63	53	31.5	1.68	16.10	0.0003
CH	6411	2	Haemorrhage from placenta previa	92	69	46	1.5	12.03	0.0035
CH	6419	2	Unspecified antepartum haemorrhage	428	274	214	1.28	17.05	0.0001
CH	6430	2	Mild hyperemesis gravidarum	1900	1116	950	1.17	29.16	0.0001
CH	6431	2	Hyperemesis gravidarum with metabolic disturbance	2079	1219	1039.5	1.17	31.15	0.0001
CH	6439	2	Unspecified vomiting of pregnancy	610	366	305	1.2	12.28	0.0031
CH	6440	2	Threatened premature labour	1169	818	584.5	1.4	95.93	0.0001
CH	6441	2	Other threatened labour	152	120	76	1.58	27.13	0.0001
CH	6442	2	Early onset of delivery	177	129	88.5	1.46	19.24	0.0001
CH	6468	2	Other specified complications of pregnancy	404	299	202	1.48	48.56	0.0001
CH	6469	2	Unspecified complication of pregnancy	558	418	279	1.5	72.45	0.0001
CH	6480	2	Diabetes mellitus conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium	74	59	37	1.59	13.99	0.0006
CH	6482	2	Anaemia conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium	222	151	111	1.36	14.74	0.0003
CH	6489	2	Other current conditions classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium	385	297	192.5	1.54	59.91	0.0001
CH	6510	2	Twin pregnancy	176	148	88	1.68	44.88	0.0001
CH	6522	2	Breech presentation without mention of version	355	284	177.5	1.6	68.42	0.0001
CH	6542	2	Previous caesarean delivery NOS	326	238	163	1.46	35.84	0.0001
CH	6558	2	Other known or suspected foetal abnormality, not elsewhere classified, affecting management of mother	169	157	84.5	1.86	73.84	0.0001
CH	6563	2	Foetal distress affecting management of mother	105	82	52.5	1.56	17.58	0.0001
CH	6612	2	Other and unspecified uterine inertia	113	106	56.5	1.88	52.08	0.0001

CH	6620	2	Prolonged first stage	73	56	36.5	1.53	10.98	0.0108
CH	6641	2	Second-degree perineal laceration	65	50	32.5	1.54	9.94	0.0286
CH	6670	2	Retained placenta without haemorrhage	17	17	8.5	2	11.78	0.0047
CH	6748	2	Other complications of the puerperium, not elsewhere classified	249	189	124.5	1.52	35.10	0.0001
CH	7651	2	Other preterm immaturity	114	81	57	1.42	10.43	0.0173
CH	7706	2	Transitory tachypnoea of new-born	47	39	23.5	1.66	11.14	0.008
CH	7708	2	Other respiratory problem after birth	65	51	32.5	1.57	11.19	0.0071
CH	63401	3	Abortion, complicated by genital tract and pelvic infection, incomplete	133	92	66.5	1.38	10.03	0.0266
CH	63491	3	Abortion, without mention of complication, incomplete	315	197	157.5	1.25	10.01	0.0269
CH	64000	3	Threatened abortion, unspecified as to episode of care or not applicable	2266	1344	1133	1.19	39.53	0.0001
CH	64001	3	Threatened abortion, delivered, with or without mention of antepartum condition	215	165	107.5	1.53	32.42	0.0001
CH	64003	3	Threatened abortion, antepartum condition or complication	3868	2321	1934	1.2	77.97	0.0001
CH	64090	3	Unspecified haemorrhage in early pregnancy, unspecified as to episode of care or not applicable	688	406	344	1.18	11.24	0.0065
CH	64101	3	Placenta previa without haemorrhage, delivered, with or without mention of antepartum condition	46	41	23	1.78	16.07	0.0003
CH	64193	3	Unspecified antepartum haemorrhage, antepartum condition or complication	329	209	164.5	1.27	12.19	0.0033
CH	64300	3	Mild hyperemesis gravidarum, unspecified as to episode of care or not applicable	1291	773	645.5	1.2	25.35	0.0001
CH	64310	3	Hyperemesis gravidarum with metabolic disturbance, unspecified as to episode of care or not applicable	254	162	127	1.28	9.77	0.0343
CH	64313	3	Hyperemesis gravidarum with metabolic disturbance, antepartum condition or complication	1802	1041	901	1.16	21.84	0.0001
CH	64393	3	Unspecified vomiting of pregnancy, antepartum condition or complication	248	162	124	1.31	11.83	0.0041
CH	64400	3	Threatened premature labour, unspecified as to episode of care or not applicable	356	268	178	1.51	47.68	0.0001
CH	64403	3	Threatened premature labour, antepartum condition or complication	813	550	406.5	1.35	51.77	0.0001
CH	64410	3	Other threatened labour, unspecified as to episode of care or not applicable	68	58	34	1.71	18.74	0.0001
CH	64413	3	Other threatened labour, antepartum	84	62	42	1.48	9.92	0.029

			condition or complication							
CH	64421	3	Early onset of delivery, delivered, with or without mention of antepartum condition	168	124	84	1.48	19.84	0.0001	
CH	64680	3	Other specified complications of pregnancy, unspecified as to episode of care or not applicable	213	179	106.5	1.68	54.12	0.0001	
CH	64690	3	Unspecified complication of pregnancy, unspecified as to episode of care or not applicable	408	314	204	1.54	62.59	0.0001	
CH	64893	3	Other current conditions classifiable elsewhere in the mother, but complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	269	217	134.5	1.61	54.38	0.0001	
CH	65100	3	Twin pregnancy, unspecified as to episode of care or not applicable	50	41	25	1.64	11.09	0.01	
CH	65101	3	Twin pregnancy, delivered, with or without mention of antepartum condition	75	63	37.5	1.68	19.01	0.0001	
CH	65103	3	Twin pregnancy, antepartum condition or complication	51	44	25.5	1.73	14.95	0.0003	
CH	65221	3	Breech presentation without mention of version, delivered, with or without mention of antepartum condition	300	249	150	1.66	71.18	0.0001	
CH	65421	3	Previous caesarean delivery NOS, delivered with or without mention of antepartum condition	298	221	149	1.48	36.29	0.0001	
CH	65581	3	Other known or suspected foetal abnormality, not elsewhere classified, affecting management of mother, delivered, with or without mention of antepartum condition	162	150	81	1.85	69.51	0.0001	
CH	65630	3	Foetal distress affecting management of mother, unspecified as to episode of care or not applicable	36	31	18	1.72	10.45	0.0168	
CH	66120	3	Other and unspecified uterine inertia, unspecified as to episode of care or not applicable	110	103	55	1.87	50.19	0.0001	
CH	66201	3	Prolonged first stage, delivered, with or without mention of antepartum condition	73	56	36.5	1.53	10.98	0.0108	
CH	66411	3	Second-degree perineal laceration, delivered, with or without mention of antepartum condition	65	50	32.5	1.54	9.94	0.0286	
CH	66700	3	Retained placenta without haemorrhage, unspecified as to episode of care or not	17	17	8.5	2	11.78	0.0047	

	CH	67480	3	applicable Other complications of the puerperium, not elsewhere classified, unspecified as to episode of care or not applicable	249	189	124.5	1.52	35.10	0.0001
	CH	V22	1	Normal pregnancy	2859	1826	1429.5	1.28	111.43	0.0001
	CH	V221	2	Supervision of other normal pregnancy	2040	1353	1020	1.33	110.73	0.0001
	CH	V24	1	Postpartum care and examination	642	397	321	1.24	18.17	0.0001
	CH	V242	2	Care and examination of routine postpartum follow-up	488	306	244	1.25	15.93	0.0003
	CH	V27	1	Outcome of delivery	1090	818	545	1.5	143.14	0.0001
	CH	V270	2	Outcome of delivery single liveborn	1022	762	511	1.49	128.80	0.0001
	CH	V272	2	Outcome of delivery twins, both liveborn	46	38	23	1.65	10.63	0.0139
	CH	V30	1	Single liveborn	123	89	61.5	1.45	12.74	0.0019
	CH	V300	2	Single liveborn, born in hospital	123	89	61.5	1.45	12.74	0.0019
	CH	V31	1	Twin, mate liveborn	31	27	15.5	1.74	9.57	0.0466
	CH	V310	2	Twin, mate liveborn, born in hospital	31	27	15.5	1.74	9.57	0.0466
	CH	V724	2	Pregnancy examination or test, pregnancy unconfirmed	2740	1548	1370	1.13	23.19	0.0001
Musculoskeletal System	CH	721	1	Spondylosis and allied disorders	28326	14745	14163	1.04	23.92	0.0001
	ADRr	723	1	Other disorders of cervical region	11131	5963	5565.5	1.07	28.41	0.0001
	ADRr	724	1	Other and unspecified disorders of back	70533	38071	35266.5	1.08	223.26	0.0001
	ADRr	847	1	Sprains and strains of other and unspecified parts of back	17733	9435	8866.5	1.06	36.48	0.0001
	ADRr	7170	2	Old bucket handle tear of medial meniscus	210	165	105	1.57	36.45	0.0001
	ADR	7180	2	Articular cartilage disorder	472	310	236	1.31	23.60	0.0001
	ADRr	7201	2	Spinal enthesopathy	572	342	286	1.2	11.04	0.0102
	ADRr	7210	2	Cervical spondylosis without myelopathy	6446	3399	3223	1.05	9.62	0.0446
	ADRr	7231	2	Cervicalgia	5883	3160	2941.5	1.07	16.25	0.0003
	ADR	7242	2	Lumbago	31911	17786	15955.5	1.11	210.47	0.0001
	ADRr	7243	2	Sciatica	10319	5449	5159.5	1.06	16.25	0.0003
	ADR	7245	2	Backache, unspecified	20573	10826	10286.5	1.05	28.31	0.0001
	ADR	7270	2	Synovitis and tenosynovitis	23713	12231	11856.5	1.03	11.83	0.0041
	ADRr	8470	2	Sprains and strains of neck	6080	3279	3040	1.08	18.81	0.0001
	ADRr	8472	2	Sprains and strains of lumbar	8401	4417	4200.5	1.05	11.16	0.0079
	ADRr	71619	3	Traumatic arthropathy, multiple sites	132	121	66	1.83	53.63	0.0001
	ADR	71800	3	Articular cartilage disorder, unspecified site	324	228	162	1.41	27.69	0.0001
	ADR	71945	3	Pain in joint, pelvic region and thigh	1188	712	594	1.2	23.60	0.0001
	ADRr	71960	3	Other symptoms referable to joint, unspecified site	623	366	311.5	1.17	9.58	0.0455
	Examinations	ADR	72700	3	Synovitis and tenosynovitis, unspecified	15651	8164	7825.5	1.04	14.65
CH		V148	2	Personal history of allergy to other specified medicinal agents	86	65	43	1.51	11.81	0.0042
CH		V53	1	Fitting and adjustment of other device	555	425	277.5	1.53	82.59	0.0001

Others	CH	V584	2	Encounter for other aftercare following surgery	1442	985	721	1.37	98.95	0.0001
	CH	V5841	3	Encounter for planned postoperative wound closure	391	261	195.5	1.34	22.38	0.0001
	CH	V5849	3	Other specified aftercare following surgery	1051	724	525.5	1.38	76.87	0.0001
	CH	V65	1	Other persons seeking consultation without complaint or sickness	1906	1077	953	1.13	16.18	0.0003
	CH	V654	2	Other counselling, not elsewhere classified	1742	1025	871	1.18	27.37	0.0001
	CH	V6540	3	Counselling, not otherwise specified	1389	855	694.5	1.23	37.43	0.0001
	CH	V72	1	Special investigations and examinations	7122	4252	3561	1.19	134.94	0.0001
	CH	922	1	Contusion of trunk	16986	8806	8493	1.04	11.54	0.0055
	CH	999	2	Complications of medical care, not elsewhere classified	255	164	127.5	1.29	10.60	0.0141
	CH	2709	2	Unspecified disorder of amino-acid metabolism	49	41	24.5	1.67	12.16	0.0033
	CH	2739	2	Unspecified disorder of plasma protein metabolism	72	57	36	1.58	13.06	0.0014
	CH	2779	2	Unspecified disorder of metabolism	648	398	324	1.23	17.05	0.0001
	CH	4556	2	Unspecified haemorrhoids without mention of complication	9103	4800	4551.5	1.05	13.57	0.0009
	CH	4564	2	Scrotal varices	637	393	318.5	1.23	17.59	0.0001
	ADR	7820	2	Disturbance of skin sensation	535	318	267.5	1.19	9.59	0.0454
	ADRr	7842	2	Swelling, mass, or lump in head and neck	1982	1118	991	1.13	16.32	0.0003
	ADR	7847	2	Epistaxis	7627	4063	3813.5	1.07	16.34	0.0003
	Ir	7864	2	Abnormal sputum	2635	1504	1317.5	1.14	26.49	0.0001
	Ir	8732	2	Other open wound of nose, without mention of complication	282	206	141	1.46	31.13	0.0001
	ADR	78071	3	Chronic fatigue syndrome	2154	1254	1077	1.16	29.22	0.0001
	Ir	87322	3	Open wound of nasal cavity, without mention of complication	117	107	58.5	1.83	46.94	0.0001

*Clinical classification was expressed in either disease or medication system.

†Node was expressed in ICD9 diagnostic codes.

Abbreviation: ADR=known adverse drug reaction; ADRr=events related to known adverse drug reaction; CH=cohort-related; I=indication; Ir=indication-related; LLR=log likelihood ratio; PT=protopathic bias; RR=relative risk.

Supplementary Table 4. Risk profile of SGLT2 inhibitors

SOC, safety concern	Preferred Terms	PBRER	Dapagliflozin		Empagliflozin		
			Warnings and precautions	Adverse reactions	PBRER	Warnings and precautions	Adverse reactions
Gastrointestinal disorders							
<i>EU RMP-Important potential risks</i>	Pancreatitis (Empagliflozin)						
	Dry mouth			EMA-uncommon			
	Constipation			EMA-uncommon USFDA-CT TFDA-CT			
	Nausea		EMA-DKA symptoms	USFDA-CT TFDA-CT		EMA-DKA symptoms	USFDA-CT TFDA-CT
	Vomiting		EMA-DKA symptoms USFDA-DKA symptoms			EMA-DKA symptoms	
	Abdominal pain		EMA-DKA symptoms USFDA-DKA symptoms			EMA-DKA symptoms	
General disorders and administration site conditions							
	Thirst		EMA-DKA symptoms	EMA-uncommon			CCDS EMA-common USFDA-CT TFDA-CT
Hepatobiliary disorders							
<i>EU RMP-Important potential risks</i>	Liver injury	Important potential risks	EMA		Important potential risks	EMA	
Immune system disorders							
	Hypersensitivity reactions	Important potential risks		USFDA-CT TFDA-CT		USFDA TFDA	USFDA TFDA
Infections and infestations							
	Urinary tract infection (including pyelonephritis, urosepsis, genitourinary tract infection, cystitis, pyelonephritis, trigonitis, urethritis and prostatitis.)	Important identified risks	EMA USFDA TFDA	CCDS-common EMA-common USFDA TFDA	Important identified risks	CCDS EMA USFDA TFDA	CCDS EMA-common USFDA TFDA

	Genital infection (Vaginal moniliasis, vulvovaginitis, balanitis, vulvovaginal infections and candidiasis, balanoposthitis, balanitis candida, penile abscess, penile infection, vulval abscess and vaginitis bacterial.)		USFDA TFDA	CCDS-common EMA-common USFDA TFDA A	Important identified risks	USFDA TFDA	CCDSEMA-common USFDA TFDA
	Upper respiratory tract infection						USFDA-CT TFDA-CT
	Necrotizing fasciitis (Fournier's gangrene)		EMA TFDA	EMA-very rare USFDA-PMS TFDA		CCDS EMA USFDA TFDA	CCDS EMA-unknown USFDA TFDA
	Nasopharyngitis			USFDA-CT TFDA-CT			
	Influenza			USFDA-CT TFDA-CT			
Injury, poisoning and procedural complications							
	Bone fracture (Empagliflozin-EU-RMP only · Dapagliflozin)	Important potential risks			Important potential risks		
Investigations							
	Clinical consequences of increased haematocrit (Dapagliflozin)	Important potential risks		EMA-common USFDA-CT TFDA-CT		EMA	CCDS EMA-uncommon USFDA-CT TFDA-CT
	Increases in Serum Creatinine			EMA-common USFDA-CT TFDA-CT			CCDS EMA-uncommon
	Decreases in EGFR			EMA-common USFDA-CT TFDA-CT			CCDS EMA-uncommon
	Decrease in Serum Bicarbonate			USFDA-CT TFDA-CT			
	Serum lipids increased (total cholesterol · HDL-cholesterol · LDL-cholesterol)			EMA-common USFDA-CT TFDA-CT		USFDA	CCDS EMA-common USFDA TFDA
	Blood urea increased			EMA-uncommon			
	Weight decreased			EMA-uncommon			
	Glucose urine present		EMA	TFDA-interaction			
Metabolism and nutrition disorders							
	Diabetic ketoacidosis (Signs and symptoms at presentation were consistent with dehydration and	Important potential risks	EMA USFDA TFDA	CCDS-rare EMA-rare USFDA TFDA	Important	CCDSEMA USFDA TFDA	CCDSEMA-rare USFDA TFDA

	severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath)				identified risks		
	Volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope)	Important potential risks	CCDS EMA USFDA	EMA-uncommon USFDA TFDA-CT	Important identified risks	CCDS EMA	CCDS EMA-uncommon USFDA-CT TFDA-CT
	Hypoglycaemia (with insulin and/or SU)		CCDS EMA-Interaction USFDA TFDA	EMA-very common USFDA TFDA	Important identified risks	USFDA TFDA	CCDS EMA-very common USFDA TFDA
	Dyslipidaemia			EMA-common USFDA-CT TFDA-CT			
Musculoskeletal and connective tissue disorders							
	Back pain			CCDS-common EMA-common USFDA-CT TFDA-CT			
	Arthralgia						USFDA-CT TFDA-CT
	Pain in extremity			USFDA-CT TFDA-CT			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
EU RMP- Important potential risks	Bladder cancer (Dapagliflozin)	Important potential risks					
	Urinary tract carcinogenicity (Bladder cancer, renal cancer) (Empagliflozin)				Important potential risks		
	Breast cancer (Dapagliflozin)	Important potential risks					
	Prostate cancer (Dapagliflozin)						
Nervous system disorders							
	dizziness			EMA-common			
Renal and urinary disorders							

	Renal impairment/renal failure	Important potential risks	EMA	EMA-common		CCDSEMAUSFDA TFDA	USFDATFDA
	Pollakiuria			CCDS-common EMA-common USFDA-CT			CCDS EMA-common USFDA-CT TFDA-CT
	Polyuria			CCDS-common EMA-common USFDA-CT TFDA-CT			CCDS EMA-common USFDA-CT TFDA-CT
	Dysuria			EMA-common USFDA-CT TFDA-CT			CCDS EMA-uncommon
	Nocturia			EMA-uncommon			CCDS EMA-common USFDA-CT TFDA-CT
	Acute Kidney Injury		TFDA	USFDA-PMS TFDA		USFDA TFDA	USFDA TFDA
Reproductive system and breast disorders							
	Vulvovaginal pruritus			EMA-uncommon			
	Pruritus genital			EMA-uncommon			
Respiratory, thoracic and mediastinal disorders							
	Shortness of breath		EMA-DKA symptoms USFDA-DKA symptoms			EMA-DKA symptoms	
Skin and subcutaneous tissue disorders							
	Angioedema			EMA-very rare		USFDA TFDA	CCDS EMA-unknown USFDA-PMS TFDA-PMS
	Skin reaction (rash, urticaria)			CCDS- unknownEMA- commonUSFDA- PMSTFDA-PMS			CCDSEMA- commonUSFDA- PMSTFDA-PMS
Surgical and medical procedures							
EU RMP- Important potential risks	Lower limb amputation		EMA USFDA		Important potential risks	EMA	
Vascular disorders							
	hypotension		TFDA EMA	USFDA TFDA		USFDA TFDA	USFDA TFDA

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), or very rare ($< 1/10,000$), and not known (cannot be estimated from the available data).

Dapagliflozin	CCDS (2018/12/7)	
	EMA(2020/1/14)	
	USFDA (2020/5)	
	TFDA (2020/3)	
	PBRER (2018/10/5-2019/10/4)	
Empagliflozin	CCDS (2018/9/24)	
	EMA (2020/5/26)	
	USFDA (2020/1)	
	TFDA (USPI 2018/10)	
	PBRER (2018/10/5~2019/10/4)	

Supplementary Table 5. Risk profile of FQs and NFQs

		Non-fluoroquinolone						Fluoroquinolone					
		Nemonoxacin		Pipemidic acid		Nalidixic acid		Levofloxacin		Ciprofloxacin		Moxifloxacin	
SOC, Safety concerns	Preferred Terms	W/P	ADR	W/P	ADR	W/P	ADR	W/P	ADR	W/P	ADR	W/P	ADR
Blood and lymphatic system disorders													
	Agranulocytosis							USFDA	USFDA-uncommon UK-unk	USFDA	UK-Very Rare	USFDA	USFDA-PME UK-Very Rare
	Anemia, including hemolytic and aplastic							USFDA	USFDA-PME UK-unk	USFDA	UK-rare	USFDA	USFDA-common UK-uncommon
	Leukopenia		TFDA-common		TFDA			USFDA	UK-uncommon USFDA-PME	USFDA	UK-rare	USFDA	USFDA-uncommon UK-uncommon
	Pancytopenia							USFDA	USFDA-PME UK-unk	USFDA	USFDA-PME UK-Very Rare	USFDA	USFDA-PME UK-Very Rare
	Thrombocytopenia, including thrombotic thrombocytopenic purpura				TFDA			USFDA	USFDA-uncommon UK-rare	USFDA	UK-rare	USFDA	USFDA-uncommon UK-uncommon
	Bone marrow depression										UK-Very Rare		
	Eosinophilia										UK-uncommon		USFDA-uncommon UK-uncommon
	Leucocytosis												USFDA-uncommon
	Methemoglobinemia										USFDA-PME		
	Neutropenia		TFDA-common						UK-rare		UK-uncommon		USFDA-uncommon UK-uncommon
Cardiac disorders													
	Torsade de pointes	TFDA						USFDA	USFDA-PME UK-unk	USFDA/UK	USFDA-PME	USFDA	USFDA-PME UK-Very Rare
	Angina Pectoris										USFDA-uncommon		USFDA-uncommon UK-uncommon

	Atrial fibrillation												USFDA-uncommon UK-uncommon						
	Bradycardia												USFDA-uncommon						
	Cardiac failure												USFDA-uncommon						
	Cardiac arrest								USFDA-uncommon UK-unk		USFDA-uncommon		USFDA-uncommon						
	Myocardial Infarction										USFDA-uncommon								
	Palpitation								USFDA-uncommon UK-rare				USFDA-uncommon UK-uncommon						
	Tachycardia								USFDA-PME UK-rare		USFDA-uncommon UK-rare		USFDA-uncommon UK-uncommon						
	Ventricular arrhythmia								USFDA-uncommon		USFDA-PME		USFDA-PME UK-rare						
	Ventricular tachycardia								USFDA-uncommon UK-unk										
Eye disorders																			
	<u>Vision disorders/ vision disturbance (including diplopia, visual acuity reduced, vision blurred, transient vision loss, chromatopsia and photopsia)</u>						TFDA	UK					USFDA-PME UK-rare	UK		USFDA-uncommon UK-rare	UK		USFDA-uncommon UK-uncommon
	Scotoma												USFDA-PME						
	Nystagmus												USFDA-PME						
	Uveitis/Uveitis and bilateral acute iris transillumination												USFDA-PME						UK-Very Rare
	Retinal Detachment																		
Ear and Labyrinth Disorders																			
	Hearing impaired												UK-unk			UK-rare			USFDA-PME UK-rare

	Hearing loss							UK-unk		USFDA-uncommon UK-rare		USFDA-PME UK-rare
	Hypoacusis							USFDA-PME				
	Tinnitus							USFDA-PME UK-rare		USFDA-uncommon UK-rare		USFDA-uncommon UK-rare
	Vertigo					TFDA		USFDA-uncommon UK-uncommon		UK-rare		USFDA-uncommon UK-uncommon
Gastrointestinal disorders												
	Severe and persistent diarrhoea								UK			
	Diarrhoea		TFDA-common				TFDA	USFDA-common UK-common		USFDA-common UK-common		USFDA-common UK-common
	Dry mouth											USFDA-uncommon
	Dysphagia											UK-rare
	Esophagitis							USFDA-uncommon				
	Gastritis							USFDA-uncommon				USFDA-uncommon UK-uncommon
	Gastroenteritis							USFDA-uncommon				USFDA-uncommon
	Gastroesophageal reflux disease											USFDA-uncommon
	Gastrointestinal Bleeding									USFDA-uncommon		
	Glossitis							USFDA-uncommon				
	Intestinal Perforation									USFDA-uncommon		
	Pancreatitis							USFDA-uncommon UK-unk		USFDA-uncommon UK-Very Rare		
	Constipation							USFDA-common UK-uncommon				USFDA-common UK-uncommon
	Flatulence		TFDA-common				TFDA	UK-uncommon		UK-uncommon		USFDA-uncommon UK-uncommon

	Stomatitis								USFDA-uncommon UK-unk				UK-rare
Hepatobiliary disorders													
<i>Important potential risks</i>	Hepatic necrosis or failure							USFDA	USFDA-PME UK-unk	USFDA/UK	USFDA-PME	USFDA	USFDA-PME UK-Very Rare
	Hepatitis							USFDA	USFDA-PME UK-unk	USFDA	USFDA-uncommon UK-rare	USFDA	USFDA-PME UK-rare
	Hepatotoxicity/Hepatobiliary disorders	TFDA						USFDA/UK		USFDA		USFDA/UK	
	Jaundice							USFDA	USFDA-PME UK-unk	USFDA		USFDA	USFDA-PME UK-rare
	Abnormal hepatic function								USFDA-uncommon		USFDA-common		
	Cholestatic icterus										USFDA-UK-rare		
	Cholestatic Jaundice										USFDA-uncommon		
Infections and infestations													
	Clostridium difficile-Associated Diarrhoea/ C. difficile colitis/ Pseudomembranous colitis	TFDA						USFDA/UK	USFDA-uncommon UK-unk	USFDA		USFDA/UK	UK-rare
	Moniliasis/Fungal infection including Candida infection								USFDA-common UK-uncommon		USFDA-PME UK-uncommon		USFDA-uncommon UK-common
	Vaginitis								USFDA-common				
Investigations													
	Blood Glucose Disturbances/Dysglycaemia	TFDA		TFDA		TFDA		USFDA/UK		USFDA/UK		USFDA/UK	
	Prolongation of the QT Interval/Torsades de Pointes	TFDA						USFDA/UK	USFDA-PME UK-unk	USFDA/UK	USFDA-PME	USFDA/UK	USFDA-uncommon UK-uncommon
<i>Important potential risks</i>	Hepatic enzyme increased (including ALT/AST, alkaline phosphatase, GGT)		TFDA-common		TFDA				USFDA-uncommon UK-common		UK-uncommon		USFDA-common UK-common

	Blood amylase increased									UK-rare		USFDA-uncommon UK-uncommon	
	Blood bilirubin increased				TFDA				UK-uncoomon	UK-uncommon		UK-uncommon	
	Blood creatinine increased				TFDA				UK-uncoomon			USFDA-uncommon	
	Blood lactate dehydrogenase increased											USFDA-uncommon UK-uncommon	
	Blood triglycerides increased											USFDA-uncommon	
	Blood urea increased											USFDA-uncommon	
	Blood uric acid increased											USFDA-uncommon	
	Cholesterol elevation (serum)									USFDA-PME			
	Lipase increased											USFDA-uncommon	
	Haematocrit decreased											USFDA-uncommon	
	Prothrombin level increased											UK-Very Rare	
	Prothrombin time prolonged								USFDA-PME	USFDA-PME		USFDA-uncommon UK-uncommon	
	International normalized ratio prolonged								USFDA-PME				
	Activated partial thromboplastin time prolonged											USFDA-uncommon	
Immune system disorders													
	Stevens-Johnson Syndrome	TFDA			TFDA			USFDA/UK	USFDA-PME UK-unk	USFDA	USFDA-uncommon UK-Very Rare	USFDA/UK	USFDA-PME UK-Very Rare
	Toxic epidermal necrolysis	TFDA			TFDA			USFDA/UK	USFDA-PME UK-unk	USFDA	USFDA-uncommon UK-Very Rare	USFDA	USFDA-PME UK-Very Rare
	Allergic pneumonitis							USFDA	USFDA-PME UK-unk	USFDA		USFDA	USFDA-PME

	Hypersensitivity Reactions/Allergic reaction (including: anaphylactic/anaphylactoid reactions, anaphylactic shock, Angioedema, Laryngeal Oedema)	TFDA			TFDA	TFDA	USFDA/UK	USFDA-PME UK-rare/UK-unk	USFDA/UK	USFDA-uncommon UK-rare	USFDA/UK	USFDA-PME UK-uncommon
	Serum sickness						USFDA	USFDA-PME	USFDA	USFDA-PME UK-Very Rare	USFDA/UK	
Musculoskeletal and connective tissue disorders												
	Exacerbation of Myasthenia Gravis	TFDA		TFDA	TFDA		USFDA/UK	USFDA-PME UK-rare	USFDA/UK	USFDA-PME	USFDA/UK	USFDA-PME UK-Very Rare
Important identified risks	Tendinitis and Tendon Rupture	TFDA		TFDA	TFDA	TFDA	USFDA/UK	USFDA-PME UK-rare	USFDA/UK	USFDA-PME UK-Very Rare	USFDA/UK	USFDA-PME UK-rare/UK-Very Rare
	Musculoskeletal Disorders/Arthropathic Effects (arthropathy, arthralgia, arthritis, myalgia, tendinopathy, and gait abnormality)						USFDA	USFDA-uncommon UK-uncommon/UK-rare	USFDA	USFDA-uncommon UK-uncommon/UK-rare	USFDA	USFDA-uncommon UK-uncommon/UK-Very Rare
	Rhabdomyolysis							USFDA-PME UK-unk				UK-unk
	Increased muscle tone and cramping									UK-rare		UK-rare
	Joint Stiffness									USFDA-uncommon		
	Ligament rupture							UK-unk				
	Myoclonus									USFDA-PME		
	Muscle enzymes increased							USFDA-PME				
	Muscle injury, including rupture							USFDA-PME/UK-unk				

	Twitching										USFDA-PME		UK-rare
Nervous system disorders													
	<u>Central Nervous System Adverse Reactions</u> (seizures (convulsions), increased intracranial pressure (including pseudotumor cerebri), tremors, and light-headedness	TFDA		TFDA		TFDA		USFDA	USFDA-uncommon UK-uncommon	USFDA/UK	USFDA-uncommon USFDA-PME UK-rare/UK-Very Rare	USFDA/UK	USFDA-uncommon UK-uncommon/UK-rare
	Peripheral Neuropathy/polyneuropathy	TFDA						USFDA/UK	UK-unk	USFDA/UK	USFDA-PME	USFDA/UK	USFDA-PME UK-rare
	Ageusia/Taste disorders/ Bad Taste/Taste loss								UK-unk		USFDA-uncommon UK-uncommon		UK-uncommon
	Anosmia (smell blindness)								USFDA-PME/UK-unk		USFDA-PME		UK-rare
	Ataxia										USFDA-uncommon		
	Benign intracranial hypertension								UK-unk		UK-Very Rare		
	Dysgeusia								USFDA-PME UK-uncommon				USFDA-uncommon
	Disturbed coordination										UK-Very Rare		USFDA-PME UK-rare
	Dyskinesia								UK-unk				
	Extrapyramidal disorder								UK-unk				
	Encephalopathy								USFDA-PME				
	Hypertonia								USFDA-uncommon		USFDA-PME		
	Hyperkinesia								USFDA-uncommon				
	Hyperaesthesia												UK-Very Rare
	Hypoesthesia												USFDA-uncommon UK-rare

	Olfactory nerve disorders										UK-Very Rare		
	Paraesthesia								USFDA-uncommon UK-rare		USFDA-uncommon UK-rare		USFDA-uncommon UK-uncommon
	Parosmia								USFDA-PME UK-unk				
	Pseudotumor cerebri								USFDA-PME				
	Speech disorders												UK-rare
	Syncope						TFDA		USFDA-uncommon UK-unk		USFDA-uncommon UK-rare		USFDA-uncommon UK-rare
Psychiatric disorders													
	<u>Psychiatric Adverse Reactions</u> (toxic psychoses, hallucinations, or paranoia; depression, or suicidal thoughts/self-endangering behaviour; anxiety, agitation, restlessness, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment, Amnesia)	TFDA		TFDA		TFDA		USFDA/UK	USFDA-uncommon UK-rare/UK-unk	USFDA/UK	USFDA-PME UK-uncommon/ UK-rare	USFDA/UK	USFDA-PME UK-Very Rare
	Abnormal dreaming								USFDA-uncommon UK-rare		UK-rare		UK-rare
	Abnormal electroencephalogram (EEG)								USFDA-PME				
	Anorexia								USFDA-uncommon UK-uncommon		USFDA-uncommon UK-uncommon		USFDA-uncommon UK-uncommon

	Depersonalization										USFDA-uncommon		UK-Very Rare
	Irritability										USFDA-uncommon		
	Manic Reaction										USFDA-uncommon UK-unk		
	Paranoia								USFDA-PME		USFDA-uncommon		
	Phobia										USFDA-uncommon		
	Psychosis								USFDA-PME		USFDA-uncommon		
Renal and urinary disorders													
	Acute renal insufficiency or failure				TFDA			USFDA	USFDA-uncommon UK-rare	USFDA	USFDA-uncommon UK-rare	USFDA	USFDA-uncommon UK-rare
	Interstitial nephritis							USFDA		USFDA	USFDA-uncommon	USFDA	USFDA-PME
	Crystalluria									USFDA/UK			
	Abnormal renal function								USFDA-uncommon				UK-rare
	Dysuria												USFDA-uncommon
	Haematuria											UK-rare	
	Tubulointerstitial nephritis											UK-rare	
Social circumstances													
<i>Important identified risks</i>	Disabling and Potentially Irreversible Serious Adverse Reactions (Disability)	TFDA		TFDA		TFDA		USFDA/UK		USFDA/UK		USFDA/UK	
Skin and subcutaneous tissue disorders													
	Photosensitivity/Phototoxicity	TFDA			TFDA			USFDA/UK	USFDA-PME UK-unk	USFDA/UK	USFDA-uncommon	USFDA/UK	USFDA-PME UK-rare
	Acute Generalized Exanthematous Pustulosis (AGEP)								USFDA-PME		USFDA-PME UK-unk		UK-unk
	Drug reaction with eosinophilia and systemic							UK	UK-rare		UK-unk		

	symptoms (DRESS)												
	Dry skin												UK-uncommon
	Erythema multiforme							USFDA-PME UK-unk			USFDA-uncommon UK-Very Rare		USFDA-uncommon
	Erythema Nodosum										USFDA-uncommon UK-Very Rare		
	Fixed drug eruptions							USFDA-PME UK-rare			USFDA-PME		
	Flushing				TFDA		TFDA				USFDA-uncommon		
	Urticaria				TFDA		TFDA	USFDA-uncommon			USFDA-uncommon UK-uncommon		USFDA-uncommon UK-uncommon
	Hyperhidrosis							UK-uncoomon					USFDA-uncommon
Vascular disorders													
<i>Important potential risks</i>	Aortic Aneurysm and Dissection							USFDA/UK		USFDA/UK		USFDA/UK	
	Vasculitis							USFDA		USFDA	USFDA-PME UK-Very Rare	USFDA	UK-Very Rare
	Hypertension												USFDA-uncommon UK-rare
	Hypotension							UK-rare			USFDA-uncommon UK-rare		USFDA-uncommon UK-rare
	Leucocytoclastic vasculitis							USFDA-PME UK-unk					
	Petechia										USFDA-uncommon UK-Very Rare		
	Phlebitis							USFDA-uncommon					USFDA-uncommon
	Vasodilatation							USFDA-PME			UK-rare		UK-uncommon

General Disorders and Administration Site Conditions

	Chills												USFDA-uncommon
	Oedema								USFDA-common		UK-rare		USFDA-uncommon UK-rare
	Infusion site extravasation												USFDA-uncommon
	Injection site reaction								USFDA-common				
	Multi-organ failure								USFDA-PME				
	Asthenia								UK-uncommon				USFDA-uncommon
	Chest pain								USFDA-common				USFDA-uncommon
	Dizziness		TFDA-common				TFDA		USFDA-common UK-common		USFDA-uncommon UK-uncommon		USFDA-common UK-common
	Dyspepsia								USFDA-common UK-uncommon		UK-uncommon		USFDA-common UK-uncommon
	Headache		TFDA-common				TFDA		USFDA-common UK-common		USFDA-uncommon UK-uncommon		USFDA-common UK-common
	Lethargy						TFDA						USFDA-uncommon
	Migraine										USFDA-uncommon UK-Very Rare		
	Nausea		TFDA-common				TFDA		USFDA-common UK-common		USFDA-common UK-common		USFDA-common UK-common
	Pain (including pain in back, chest, and extremities)								UK-unk		USFDA-common UK-uncommon		USFDA-uncommon UK-uncommon
	Pyrexia								USFDA-PME UK-rare				USFDA-common
	Somnolence						TFDA		USFDA-uncommon UK-uncommon				USFDA-uncommon UK-uncommon

	Sweating										USFDA-uncommon UK-rare		USFDA-uncommon UK-uncommon
	Vomiting		TFDA-common						USFDA-common UK-common		USFDA-common UK-uncommon		USFDA-common UK-common
Respiratory, Thoracic, and Mediastinal Disorders													
	Asthma												USFDA-uncommon
	Bronchospasm								UK-unk		USFDA-uncommon		USFDA-uncommon
	Dyspnoea								USFDA-common UK-uncommon		USFDA-uncommon UK-rare		USFDA-uncommon UK-uncommon
	Epistaxis								USFDA-uncommon				
	Haemoptysis										USFDA-uncommon		
	Wheezing												USFDA-uncommon
Metabolism and nutrition disorders													
	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)								UK-rare		UK-unk		UK-Very Rare
	Dehydration												USFDA-uncommon UK-uncommon
	Hyperglycaemia								USFDA-uncommon UK-unk		USFDA-uncommon UK-rare		USFDA-uncommon UK-rare
	Hypoglycaemic coma								UK-unk				UK-Very Rare
	Hypoglycaemia								USFDA-uncommon UK-rare		USFDA-uncommon		UK-Very Rare
	Hyperkalaemia								USFDA-uncommon		USFDA-PME		
	Hyperuricaemia												UK-rare
	Hyperlipidaemia												USFDA-uncommon UK-uncommon

Frequencies of Adverse Reaction			
	USFDA	UK	TFDA
≥1/100 to <1/10	Common	Common	Common
≥1/1,000 to <1/100	Uncommon	Uncommon	x
≥1/10,000 to <1/1,000	x	Rare	x
< 1/10,000	x	Very Rare	x
other	Post marketing Experience (PME)	Unknown (unk)	x

Reference	
Nemonoxacin	TFDA (Taigexyn [®] , 2020/01)
Pipemidic acid	TFDA (Dolcol [®] , 2019/04)
Nalidixic acid	TFDA (Nagamin [®] , 2019/05)
Levofloxacin	USFDA (Levaquin [®] , 2018/10), UK (Levofloxacin [®] , 2019/11), EU-RMP (Quinsair [®] , 2020/02)
Ciprofloxacin	USFDA (Cipro [®] , 2020/05), UK (Ciproxin [®] , 2019/11)
Moxifloxacin	USFDA (Avelox [®] , 2020/05), UK (Avelox [®] , 2020/14)

Supplementary Table 6. Examples of different types of alerts

Types of alerts	Abbreviation	Example alerts in SGLT2i instance	Example alerts in NFQ instance
ADR	ADR	Genitourinary tract infections	Diarrhea
ADR-related event	ADRr	Anogenital pruritus, which is not listed as an ADR in the risk profile of SGLT2i but is likely caused by genitourinary tract infections following the use of SGLT2i.	Unspecified functional disorder of the intestine; this diagnosis may result from gastrointestinal discomfort related to use of NFQ, however it is not documented as ADR on the drug label.
Indication	I	Diabetes	Acute sinusitis
Indication-related event	Ir	Cardiovascular diseases (CVDs); some SGLT2is have been shown to decrease risk of CVDs, thus are more likely to be prescribed in patients with CVD.	Acute bronchiolitis; this event is commonly diagnosed with respiratory infection which is one of the clinical indications of NFQ.
Cohort-related event	CH	Obesity; many patients with type 2 diabetes are obese or have related risk factors.	Complications of the puerperium; NFQ is likely to be prescribed for patients with genitourinary infections, which are frequently encountered in pregnant women.
Protopathic bias	PT	(Not likely to find any because SGLT2is are seldom used for treating symptoms of any diseases.)	Benign neoplasm of the bladder; patients with bladder tumour may have presented symptoms mimicking genitourinary infections (e.g., cystitis) and were prescribed NFQ before the confirmation of the true diagnosis.

References

1. Tsiropoulos I, Andersen M, Hallas J. Adverse events with use of antiepileptic drugs: a prescription and event symmetry analysis. *Pharmacoepidemiology and drug safety*. 2009 Jun;18(6):483-91.
2. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. *British medical journal (Clinical research ed)*. 1988 May 7;296(6632):1313-6.
3. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology (Cambridge, Mass)*. 1996 Sep;7(5):478-84.
4. Lai EC, Pratt N, Hsieh CY, Lin SJ, Pottegård A, Roughead EE, et al. Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies. *European journal of epidemiology*. 2017 Jul;32(7):567-82.
5. Kulldorff M, Dashevsky I, Avery TR, Chan AK, Davis RL, Graham D, et al. Drug safety data mining with a tree-based scan statistic. *Pharmacoepidemiology and drug safety*. 2013 May;22(5):517-23.
6. Wang SV, Maro JC, Baro E, Izem R, Dashevsky I, Rogers JR, et al. Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic. *Epidemiology (Cambridge, Mass)*. 2018 Nov;29(6):895-903.