

Comparison of Safety Profiles for Dapagliflozin Based on Safety Issues of EMA and FDA: Challenges and Future of Post-Marketing Surveillance in Korea

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Step 1. Identification of AEs associated with dapagliflozin using PMS data in Korea

Detect safety signals using KAERS

- Study Period: Between January 1, 2014, and December 31, 2020
- Conducted signal detection for all reported AE of other OHAs in comparison to dapagliflozin (as Forxiga®), applying the traditional data mining method.
- Criteria for signal: Considers a signal if $PRR \geq 2$, $ROR \geq 2$, and the lower limit of the 95% CI of the IC is greater than 0.

Identification of AEs from the use-result surveillance data

- Study Period: Between November 26, 2013, and November 25, 2019
- Study population: Korean T2D patients aged 18 years or older who are treated with dapagliflozin (as Forxiga®)
- Source of AEs: "Precautions for use" section of the drug label in Korea.



Step 2. Reviewing and defining the safety issues of EMA and FDA

EMA

- Source of AEs: Safety specification of the RMP from EMA website
- Documents reviewed: 10 assessment reports on Forxiga® dated between December 7, 2012, and March 1, 2023
- Criteria for safety issue: An AE mentioned at least once in the documents

FDA

- Source of AEs: "Warnings and precautions" section of Farxiga® drug label from Drugs@FDA website
- Documents reviewed: 18 documents dated between January 8, 2014, and September 12, 2023
- Criteria for safety issue: An AE mentioned at least once in the documents



Step 3. Comparing signals from KAERS and AEs from the use-result surveillance data based on safety issues of EMA and FDA

- Based on safety issues of EMA and FDA, signals from KAERS and AEs from use-result surveillance were manually matched and compared.
- Terms from each source were converted to the WHO ART PT level.
- When AEs were identified only in signal or use-result surveillance data, they were matched based on signal from KAERS.

Supplementary Fig. S1 Research Methodology Schematic. *AE* adverse event, *CI* confidence interval, *EMA* European Medicines Agency, *FDA* Food and Drug Administration, *IC* information component, *KAERS* Korea Adverse Event Reporting System, *OHAs* oral hypoglycemic agents, *PRR* proportional reporting ratio, *PMS* post-marketing surveillance, *PT* preferred term, *RMP* risk management plans, *ROR* reporting odds ratio, *T2D* Type 2 diabetes, *WHO ART* World Health Organization Adverse Reactions Terminology

Supplementary Table S1 Use-result surveillance data for dapagliflozin as listed in the Korean drug label

The frequency of occurrence	WHO ART SOC	Serious AEs unrelated to causality	Serious ADRs where causality cannot be excluded	Unexpected AEs unrelated to causality	Unexpected ADRs where causality cannot be excluded
		1.59% (48/3,027 person, 52 cases)	0.17% (5/3,027 person, 5 cases)	15.73% (476/3,027 person, 624 cases)	3.67% (111/3,027 person, 129 cases)
Rare (less than 0.01-0.1%)	Skin and appendages disorders	-	-	Alopecia, Dermatitis, Dermatitis allergic, Dermatitis contact, Dyshidrotic eczema, Eczema, Genital wart, Hyperkeratosis, Nail pigmentation, Nummular eczema, Rash genital, Skin lesion, Tinea pedis, Xeroderma	Cold sweat, Dermatitis, Hyperkeratosis, Skin lesion, Urticaria, Xeroderma
	Musculo-skeletal system disorders	Fracture ankle, Fracture hand, Fracture pelvis, Fracture thoracic vertebrae, Fracture tibia, Ligament sprain, Meniscus injury	-	Abrasion NOS, Fibromyalgia, Fracture ankle, Fracture foot, Fracture hand, Fracture orbital, Fracture pelvis, Fracture thoracic vertebrae, Fracture tibia, Laceration, Limb discomfort, Limb injury, Meniscus injury, Muscle cramp, Musculoskeletal discomfort, Osteopenia, Tendon rupture	Muscle weakness
	Central & peripheral nervous system disorders	Nerve compression, Dysaesthesia	-	Aphonia, Diabetic neuropathy, Facial pain, Faintness, Headache vascular, Nerve compression, Neuralgia, Neuropathy peripheral, Tension headache, Tremor, Unconsciousness, Vertigo	
	Vision disorders	Keratitis	-	Allergic conjunctivitis, Blepharitis, Cataract, Chemosis, Conjunctivitis, Diplopia, Eye pain, Hordeolum, Hypertension ocular, Keratitis, Retinal disorder, Vision decreased, Visual disturbance, Vitreous floaters	
	Special senses other, disorders	-	-	Dysgeusia	Dysgeusia

Psychiatric disorders	Depression, Drug addiction, Suicide attempt	-	Anxiety disorder, Depression, Drug addiction, Erectile dysfunction, Hallucination auditory, drowsiness, Sleep disturbed, Suicide attempt	Anxiety disorder, Appetite increased
Gastro-intestinal system disorders	Abdominal pain upper, Bowel perforation, Diverticula, Diverticulitis, GERD, Pancreatitis acute, Pancreatitis chronic	-	Chronic gastritis, Colonic polyp, Diverticula, Diverticulitis, Epigastric discomfort, Flatulence, Foreign body in alimentary tract, Frequent bowel movements, Gastritis erosive, Gastroenteritis, Gum disorder, Gum pain, Haemorrhoids, Hiatus hernia, Intestinal functional disorder, Intestinal perforation, Irritable bowel syndrome, Melaena, Pancreatitis acute, Pancreatitis chronic, Pericoronitis, Tooth injury	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Frequent bowel movements, Gastritis, GI distress, Oesophagitis
Liver and biliary system disorders	Alcoholic liver disease, Bile duct stone, Cholangitis	-	Alcoholic liver disease, Bile duct stone, Cholangitis	
Metabolic and nutritional disorders	Hyperglycaemia	Hyperglycaemia	Diabetic ulcer foot, Lactate blood increase, Thyroid mass, Vitamin D deficiency, Xerophthalmia	Hyperglycaemia, Lactate blood increase, Weight increase
Endocrine disorders	-	-	Hypogonadism male, Pituitary neoplasm NOS	Pituitary neoplasm NOS
Cardiovascular disorders, general	-	-	Diastolic dysfunction	Hypotension postural
Myo-, endo-, pericardial & valve disorders	Angina pectoris, Myocardial infarction	-	Angina pectoris, Myocardial infarction	
Heart rate and rhythm disorders	-	-	Fibrillation atrial	
Vascular (extracardiac) disorders	Cerebral haemorrhage, Cerebral infarction, PAOD	-	Arteriosclerosis, Cerebral haemorrhage, Cerebral infarction, Flushing, PAOD, Peripheral coldness, Vein varicose	
Respiratory system disorders	COPD, Haemoptysis, Pneumonia, Sinusitis	-	Allergic rhinitis, Asthma, Bronchitis, COPD, Haemoptysis, Laryngitis, Nasal	

			bleeding, Oropharyngeal pain, Pneumonia, Rhinitis, Sinusitis, Sleep apnoea syndrome, Sputum, Tonsillitis, Wheezes	
White cell and reticulo-endothelial system disorders	-	-	Lymphopenia	
Platelet, bleeding & clotting disorders	-	-	Bruise	
Urinary system disorders	Urinary tract infection	Pyelonephritis acute, Urinary tract infection	Bladder irritability, Diabetic nephropathy, Enuresis, Face oedema, Microalbuminuria, Stress urinary incontinence, Ureteral calculus, Urinary hesitation, Urinary urgency	Enuresis, Urine abnormal, Urinary urgency
Reproductive disorders, male	-	-	Benign prostatic hyperplasia	
Reproductive disorders, female	Pelvic inflammation	-	Breast mass, Breast pain female, Menstrual flooding, Metrorrhagia, Pelvic inflammation, Vaginal haemorrhage, Vulvovaginal discomfort	Menstrual irregularity, Vulvovaginal discomfort
Neoplasms	Gastric adenocarcinoma	-	Erythrocytosis, Gastric adenocarcinoma, Gastric adenoma, Hepatic cyst, Neuroma, Polycythaemia, Thyroid cyst	
Body as a whole - general disorders	Anaphylactic reaction, Asthenia, Pain, Tuberculosis pulmonary	-	Anaphylactic reaction, Carpal tunnel syndrome, Fever, Flank pain, Foreign body sensation, Influenza-like symptoms, Oedema, Oedema eyelid, Oedema genital, Sensation of warmth, Tuberculosis pulmonary	Chest pain, Fatigue, Foreign body sensation, Oedema, Oedema genital, Pain
Resistance mechanism disorders	-	-	Abscess joint, Herpes simplex, Herpes zoster, Otitis media	Herpes simplex
Secondary terms - events	Road traffic accident	-	Non-drug allergy, Road traffic accident	Non-drug allergy
Infrequent (less than 0.1-1%)	Skin and appendages disorders	-	Cold sweat, Pruritus, Urticaria	Pruritus

Musculo-skeletal system disorders	-	-	Arthralgia, Ligament sprain, Muscle weakness, Musculoskeletal pain, Myalgia, Osteoarthritis	
Central & peripheral nervous system disorders	-	-	Dysaesthesia, Headache, Hypoaesthesia	Headache
Vision disorders	-	-	Retinopathy diabetic	
Hearing and vestibular disorders	-	-	Tinnitus	
Psychiatric disorders	-	-	Appetite decreased, Appetite increased, Hunger abnormal, Insomnia	Appetite decreased, Hunger abnormal
Gastro-intestinal system disorders	-	-	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Diarrhoea, Dyspepsia, Enteritis, Gastric ulcer, Gastritis, GERD, GI distress, Nausea, Oesophagitis, Vomiting	Diarrhoea, Dyspepsia, Vomiting, Nausea
Liver and biliary system disorders	-	-	SGPT increased, SGOT increased, Gallbladder polyp, Liver fatty	
Metabolic and nutritional disorders	-	-	Hyperglycaemia, Polydipsia, Weight increase	Polydipsia
Cardiovascular disorders, general	-	-	Hypotension postural	
Heart rate and rhythm disorders	-	-	Palpitation	Palpitation
Respiratory system disorders	-	-	Coughing, Dyspnoea, Nasopharyngitis, Upper respiratory tract infection	
Urinary system disorders	Pyelonephritis acute	-	Urine abnormal, Urinary retention	Urinary retention
Reproductive disorders, female	-	-	Leukorrhoea, Menstrual irregularity	Leukorrhoea
Body as a whole - general disorders	Chest pain	-	Asthenia, Chest discomfort, Chest pain, Fatigue, Oedema generalized, Oedema peripheral, Pain, Pain in limb	Asthenia

AE adverse event, *ADR* adverse drug reaction, *COPD* Chronic obstructive pulmonary disease, *GERD* gastroesophageal reflux disease, *GI* gastrointestinal, *NOS* not

otherwise specified, *PAOD* Peripheral arteriosclerotic occlusive disease, *SGOT* serum glutamic oxaloacetic, *SGPT* serum glutamic pyruvate transaminase, *WHO ART*

World Health Organization adverse reaction terminology