

# The risk of pulmonary adverse drug reactions of rebamipide and other drugs for acid-related diseases: An analysis of the national pharmacovigilance database in South Korea

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**Objective:** The objective of this case/non-case study was to detect rebamipide-related pulmonary adverse events (AE) compared with other drugs for acid-related disorders based on population-level data.

**Methods:** From 2009 to 2018, AE reports on drugs for acid-related disorders, which are anatomical therapeutic chemical code A02B drugs, in the Korea Adverse Events Reporting System (KAERS) database were examined. The reporting odds ratio (ROR) was calculated, and the odds of reporting pulmonary AE for rebamipide and all other A02B drugs were compared. Furthermore, a stratified analysis according to patients' age and sex was conducted.

**Results:** Altogether 13 (0.05%) and 157 (0.11%) cases of pulmonary AE were reported for rebamipide and all other A02B drugs, respectively. The risk of reporting pulmonary AE was significantly lower for rebamipide than for all other A02B drugs (ROR 0.49, 95% confidence interval [CI] 0.28–0.87). The number of reports of pulmonary AE for rebamipide was significantly higher among patients aged  $\geq 65$  years than those aged  $< 65$  years (ROR 19.36, 95% CI 2.50–149.97).

**Conclusions:** Rebamipide was less often reported for pulmonary AE. However, healthcare professionals need to be aware of the risk of pulmonary AE in elderly patients.

## KEYWORDS

drug-related side effects and adverse reactions, interstitial lung diseases, KIDS KAERS database, pharmacovigilance, rebamipide

## 1 | INTRODUCTION

Rebamipide is a drug developed in Japan that protects the gastrointestinal mucosa from damage.<sup>1</sup> It acts by promoting the production of prostaglandin E2 (PGE2) and secretion of mucus, scavenging ability on oxygen free radicals and through anti-inflammatory effects.<sup>1,2</sup> Rebamipide is used to treat peptic ulcer disease (PUD) and mucosal

damage induced by non-steroidal anti-inflammatory drugs (NSAIDs).<sup>2</sup> It has been widely used in the East Asia and Southeast Asia, including South Korea.

Adverse drug reactions (ADR) associated with the use of rebamipide are usually minimal or mild.<sup>3,4</sup> Gastrointestinal reactions such as nausea, vomiting, constipation, diarrhea and bloating are common ADR of rebamipide.<sup>4</sup> While lung disorders caused by rebamipide

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are rare and are currently not included in the drug label. Two case studies from Japan have reported pulmonary adverse events (AE) associated with the use of rebamipide, including pneumonitis in a 75-year-old man who received the drug for 7 months, and lung injury in a 76-year-old man.<sup>5,6</sup> However, there are no other publications with high-quality evidence on pulmonary toxicity of rebamipide. Thus, population-level studies are required to verify the results of these case studies.

AE reporting systems are widely used because they are cost-effective for the collection of information about post-marketing surveillance of AE.<sup>7</sup> The Korea Adverse Events Reporting System (KAERS) database, which was developed by the Korea Institute of Drug Safety and Risk Management (KIDS), contains reports of AE from pharmaceutical companies, national and international pharmacovigilance centers, consumers and regulatory authorities. Due to the limitations of safety information assessed via clinical trials, data in the KIDS KAERS database (KIDS-KD) have been used to detect previously unknown ADR in a real-world setting.<sup>8–10</sup>

In this study we aimed to evaluate whether rebamipide can cause pulmonary ADR. Moreover, subgroup analyses according to patients' age and sex were conducted to assess demographic risk factors for pulmonary ADR related to rebamipide use.

## 2 | MATERIALS AND METHODS

### 2.1 | Database, study drug and AE

From January 2009 to December 2018, reports of AE in the KIDS-KD about drugs used to treat PUD and gastroesophageal reflux disease (GERD) (such drugs are classed as Anatomical Therapeutic Chemical [ATC] code A02B drugs) were examined, including H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs), prostaglandins, proton pump inhibitors (PPIs) and other drugs for the treatment of PUD and GERD (A02BX). Reports on the AE related to a combination use of drugs for *Helicobacter pylori* eradication were excluded. The study protocol was exempted from review by the Institutional Review Board of Ehwa Womans University (no. ewha-202102-0009-01).

The KAERS data comprised tables of information about basic details, drugs, AE, seriousness of the AE, AE reporters, evaluation of the AE, patients' medical history, and initial and follow-up reports. The formats of AE reports are available at <https://kaers.drugsafe.or.kr/kaers/moc/eachReport/eachReportInfoExpert.do> (for health professionals) and <https://nedrug.mfds.go.kr/CCCBA03F010/getReport> (for consumers). All drugs were coded using the ATC code. The reporters recorded the drug as a suspect drug and a co-administered drug. They were able to classify the causality as “certain”, “probable”, “possible”, “unlikely”, “unclassified”, “unassessable” and “not applicable,” according to World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality categories. Since rebamipide is generally not suspected to cause AE, causality was not considered in our primary analysis. AE were coded using the preferred terms of the WHO-adverse reaction terminology (ART) version 092 code. Serious AE were defined as any AE that resulted in death, life-threatening situation, hospitalization or prolongation of existing hospitalization,

persistent or significant disability, congenital abnormality or birth defect, or other medically important conditions defined by the KIDS. Follow-up reports of initially reported AE were excluded from the analysis. It is possible that one drug may cause more than one adverse event, and one single adverse event may be caused by more than one drug. For analysis, one-to-one pairs of suspected drug-related AE were made.

The study drug, rebamipide, was defined using the ATC code A02BX14, and other drugs included as “all other A02B drugs” were defined as comparison drugs. The definitions of pulmonary AE used in this study are listed in Table 1, and the remaining AE are defined as “other AE”.

### 2.2 | Statistical analysis

A descriptive analysis was conducted to determine the characteristics of the AE reports, including patients' demographics (sex and age), type of the reporter, and the seriousness of the AE. The number and percentage of the reports about rebamipide and all other A02B drugs were calculated.

A disproportionality analysis was conducted. The reporting odds ratio (ROR) and 95% confidence interval (CI) were calculated such that the odds of reporting pulmonary AE for rebamipide and pulmonary AE for all other A02B drugs could be compared.<sup>11</sup> Because age and sex can affect pulmonary toxicity, a stratified analysis according to patients' age (<65 y or ≥65 y) and sex was conducted.

Furthermore, we conducted sensitivity analyses to assess the consistency of the results. First, rebamipide (A02BX14) was compared with other A02BX drugs (eg, sucralfate, bismuth subcitrate/subnitrate, sulglicotide, tropixide and alginic acid). The comparisons in the fourth

**TABLE 1** Definition of pulmonary adverse events based on the Adverse Reaction Terminology version 092 code

ARRN	SEQ	Preferred terms
0529	001	Pulmonary eosinophilia
	003	Loeffler's syndrome
	004	Pneumonitis allergic
	005	Pneumonia eosinophilic
0532	001	Pulmonary fibrosis
	003	Lung fibrosis interstitial
1038	001	Pulmonary infiltration
	003	Lung infiltration
	004	Interstitial lung disease
	005	Pneumonia interstitial
	1141	001
003		Rales
004		Pulmonary irritation
005		Aspiration pneumonitis
006		Chemical pneumonitis

Abbreviations: ARRN, adverse reaction record number; SEQ, sequence number.

level of the ATC code aimed to exclude the effects of other classes, H<sub>2</sub>RAs, prostaglandins and PPIs on statistical analysis and confirm the robustness of the results. Second, we evaluated whether the results were maintained even if the AE judged by the reporter to be “unlikely” were excluded from the analysis. Third, AE classified as “certain”, “probable” and “possible” were analyzed.

All the statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). A *P* value of <0.05 was considered statistically significant.

### 3 | RESULTS

There were 16 601 AE reports on rebamipide and 77 897 on all other A02B drugs. The characteristics of the AE reports in the KIDS-KD are

**TABLE 2** Characteristics of adverse events (AE) reports in the Korea Adverse Events Reporting System database (2009–2018)

Characteristics, n (%)	Rebamipide (n = 16 601)	All other A02B drugs (n = 77 897)
<b>Sex</b>		
Male	5953 (35.86)	29 590 (37.99)
Female	10 463 (63.03)	47 184 (60.57)
NA	185 (1.11)	1123 (1.44)
<b>Age (y)</b>		
0–19	275 (1.66)	1693 (2.17)
20–39	1829 (11.02)	9135 (11.73)
40–64	7646 (46.06)	34 969 (44.89)
≥65	5597 (33.71)	23 412 (30.06)
NA	1254 (7.55)	8688 (11.15)
<b>Reporters</b>		
Physician	5602 (33.74)	33 131 (42.53)
Pharmacist	8602 (51.82)	20 136 (25.85)
Nurse	972 (5.85)	15 984 (20.52)
Consumer	247 (1.49)	1456 (1.87)
Others	270 (1.63)	2298 (2.95)
Unknown	908 (5.47)	4892 (6.28)
<b>Severity of AE</b>		
Serious <sup>a</sup>	1438 (8.66)	8412 (10.80)
Death	118 (0.71)	1087 (1.40)
Life-threatening	27 (0.16)	247 (0.32)
Hospitalization	1091 (6.57)	5703 (7.32)
Disability or permanent damage	9 (0.05)	57 (0.07)
Congenital anomaly or birth defect	1 (0.006)	2 (0.003)
Others	337 (2.03)	2167 (2.78)
Non-serious	15 163 (91.34)	69 485 (89.20)

<sup>a</sup>Types of serious AE (death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly or birth defect, and other serious events) may be duplicated.

Abbreviation: NA, not available.

presented in Table 2. About 60% of the total AE cases occurred in female patients. And approximately 90% of the AE caused by drugs, including rebamipide, were not serious. A total of 24 980 rebamipide-related AE and 148 601 all other A02B drugs–AE pairs were retrieved from the reports. In patients aged <65 years, 14 479 rebamipide–AE pairs were identified, while 8 238 rebamipide–AE pairs were identified in patients aged ≥65 years. Frequently reported AE that were found to be paired with rebamipide are listed in Table 3.

In total 13 (0.05%) cases of pulmonary AE related to the use of rebamipide were reported compared with 157 (0.11%) related to all other A02B drugs (Table 4). The risk of pulmonary AE was significantly lower for rebamipide than for all other A02B drugs (ROR 0.49, 95% CI 0.28–0.87). The low ROR remained significant when comparing rebamipide with other A02BX drugs (ROR 0.37, 95% CI 0.19–0.74) and when AE were classified as “unlikely” were excluded (ROR 0.49, 95% CI 0.27–0.89). Only three cases of “certain”, “probable” and “possible” pulmonary AE were reported for other A02B drugs, compared with one case for rebamipide, indicating no statistically significant differences (ROR 2.28, 95% CI 0.21–25.16).

There were more reported pulmonary AE associated with rebamipide in men and in patients aged ≥65 years than in women and in those aged <65 years. Subgroup analysis according to patients’ age and sex showed that fewer pulmonary AE were reported for rebamipide than for all other A02B drugs, although this effect was not statistically significant (Table 4). A further analysis was conducted

**TABLE 3** Frequently reported adverse events (AE) associated with rebamipide and other A02B drugs

AE	n (%)
<b>Rebamipide (n = 24 980)</b>	
Dyspepsia	1505 (6.02)
Dizziness	1331 (5.33)
Nausea	1322 (5.29)
Somnolence	1285 (5.14)
Diarrhea	1103 (4.42)
Pruritus	902 (3.61)
Rash	884 (3.54)
Constipation	734 (2.94)
Insomnia	661 (2.65)
Vomiting	651 (2.61)
<b>All other A02B drugs (n = 148 601)</b>	
Nausea	12 211 (8.22)
Dizziness	6665 (4.49)
Pruritus	5724 (3.85)
Vomiting	5183 (3.49)
Rash	4850 (3.26)
Dyspepsia	4563 (3.07)
Diarrhea	4288 (2.89)
Abdominal pain	3416 (2.30)
Urticaria	3280 (2.21)
Constipation	2829 (1.90)

to assess the increased risk of pulmonary AE in the elderly. The risk of reporting pulmonary AE was significantly higher for rebamipide in patients aged  $\geq 65$  years than in those aged  $< 65$  years (ROR 19.36, 95% CI 2.50–149.97; Table 5). However, a similar trend was observed for all other A02B drugs (ROR 4.29, 95% CI 2.96–6.23; Table 5).

Due to the low frequency of pulmonary AE among all AE, an analysis of pulmonary AE among serious AE was conducted. There were 10 (0.44%) serious pulmonary AE among 2274 rebamipide-related serious AE. Details of the patients who took rebamipide and reported serious pulmonary AE are shown in Table 6. In all other A02B drugs, 94 (0.53%) serious pulmonary AE were reported among 17 724 all

**TABLE 4** Reporting odds ratio (ROR) of pulmonary adverse events

	Rebamipide, n/N (%)	All other A02B drugs, n/N (%)	ROR (95% CI)
Total	13/24 980 (0.05)	157/148 601 (0.11)	0.49 (0.28–0.87)
Age			
<65 y	1/14 479 (0.007)	40/84 776 (0.05)	0.15 (0.02–1.06)
$\geq 65$ y	11/8238 (0.13)	90/44 524 (0.20)	0.66 (0.35–1.24)
Sex			
Male	8/9344 (0.09)	88/59545 (0.15)	0.58 (0.28–1.19)
Female	5/15356 (0.03)	61/87222 (0.07)	0.46 (0.19–1.16)

Abbreviation: CI, confidence interval.

**TABLE 5** Differences in the risk of pulmonary adverse events (AE) by age

Drugs	AE, n (%)	Age $\geq 65$ years	Age $< 65$ years	ROR (95% CI)
Rebamipide	Total	8238	14 479	19.36 (2.50–149.97)
	Pulmonary AE	11 (0.13)	1 (0.007)	
	Other AE	8227 (99.87)	14 478 (99.993)	
All other A02B drugs	Total	44 524 (100)	84 776 (100)	4.29 (2.96–6.23)
	Pulmonary AE	90 (0.20)	40 (0.05)	
	Other AE	44 434 (99.80)	84 736 (99.95)	

Abbreviations: CI, confidence interval; ROR, reporting odds ratio.

**TABLE 6** Serious pulmonary adverse events reported in patients receiving rebamipide

ARRN	Type of seriousness	Sex, age (y)	Drugs <sup>a</sup>	Medical history
0532	Death	Male, $\geq 65$	HMG-CoA reductase inhibitor combination, magnesium, clopidogrel, escitalopram, polycarbophil calcium, rebamipide	Depression, hypertension, cerebral infarction, other functional gastrointestinal disorder
1038	Other serious AE	Male, 82	Quetiapine, platelet aggregation inhibitors, ceftriaxone, clindamycin, clopidogrel, mannitol, naloxone, rebamipide, thiamine	NA
	Hospitalization, Other serious AE	Female, 74	Abatacept, alendronic acid and colecalciferol, celecoxib, folic acid, lansoprazole, methotrexate, rebamipide	NA
	Death, Hospitalization	Male, 77	Hydromorphone, xanthines, codeine, docetaxel, famotidine, glimepiride, magnesium hydroxide, nicorandil, rebamipide, tramadol, tramadol and paracetamol	NA
1141	Hospitalization	Female, 60	Macitentan, calcium combinations with vitamin D and/or other drugs, phosphodiesterase inhibitors, acetylsalicylic acid, deflazacort, digoxin, esomeprazole, febuxostat, ferrous sulfate, furosemide, levothyroxine sodium, mycophenolic acid, rebamipide, spironolactone	Hypothyroidism, depression, sleep disorder, tricuspid valve disease, GERD, SLE, acute nephritic syndrome

(Continues)

TABLE 6 (Continued)

ARRN	Type of seriousness	Sex, age (y)	Drugs <sup>a</sup>	Medical history
	Hospitalization, Other serious AE	Male, 75	Afatinib, digestives (including enzymes), H <sub>2</sub> -receptor antagonists, cefalexin, cefditoren, rebamipide	Pneumonia, gastritis, nail disorder, rash and skin eruption, postsurgical state
	Hospitalization	Female, 77	Afatinib, bisoprolol, doxofylline, famotidine, ramipril, rebamipide, rosuvastatin	Angina pectoris, asthma, rib fracture
	Death	Male, 77	Imipenem/cilastatin, enzymes, acetylcysteine, cefepime, furosemide, levofloxacin, ornidazole, piperacillin/beta-lactamase inhibitor, ranitidine, rebamipide, tamsulosin, vancomycin	Esophageal malignancy, diabetes mellitus
	Death	Female, 85	Losartan/amlodipine, appetite stimulants, vitamin B complex with vitamin C, amikacin, ceftriaxone, donepezil, folic acid, magnesium hydroxide, metformin, rebamipide	NA
	Hospitalization	Male, 76	Cilostazol, probucol, buspirone, carvedilol, choline alfoscerate, clonazepam, rebamipide, zolpidem	Hypertension, angina pectoris, cerebral infarction, dizziness, shoulder and upper arm fracture

Abbreviations: ARRN, adverse reaction record number; GERD, gastroesophageal reflux disease; HMG-CoA,  $\beta$ -hydroxy  $\beta$ -methylglutaryl coenzyme A; NA, not available; SLE, systemic lupus erythematosus.

<sup>a</sup>The first drugs were recorded as suspect drugs by the reporter and the rest as co-administered drugs.

other A02B drugs-related serious AE. There was no statistically significant difference (ROR 0.83, 95% CI 0.43–1.59).

## 4 | DISCUSSION

This study investigated the relationship between rebamipide and pulmonary AE using a national pharmacovigilance database in South Korea. Contrary to the hypothesis of this study, use of rebamipide was not associated with an increased risk of AE compared with other drugs of the same class.

There was a significantly lower risk of pulmonary AE associated with the use of rebamipide compared with that with other drugs to treat PUD and GERD. Drugs used to treat PUD and GERD have a low risk of developing pulmonary AE. The labels of only three drugs, famotidine, lansoprazole and rabeprazole, mention interstitial pneumonia as a rare ADR. The reasons why rebamipide is associated with a lower risk of AE than all other A02B drugs can be explained as follows. First, although the mechanism has not been completely understood, rebamipide has anti-inflammatory effects on the lungs. In a mouse model, the scores for inflammation and goblet cell hyperplasia of lung tissues were significantly lower in the rebamipide group than in the control group.<sup>12</sup> Rebamipide reduced the expressions of inflammatory cytokines including interleukin (IL)-4, IL-5, IL-13, IL-33 and tumor necrosis factor (TNF)- $\alpha$ .<sup>4,12,13</sup> Furthermore, PGE2 has beneficial effects on pulmonary inflammation and fibrosis.<sup>14</sup> Rebamipide increases PGE2 levels; therefore, the risk of pulmonary AE may be low in patients receiving rebamipide. However, there are few studies on the effects of rebamipide on the lungs. H<sub>2</sub>RAs, prostaglandins and PPIs may have similar mechanisms. Further studies are needed to confirm our results. Second, H<sub>2</sub>RA and PPIs increase the risk of infectious pneumonia.<sup>15–17</sup>

Famotidine, lansoprazole and rabeprazole lower the acidity of the stomach, which can cause bacterial colonization and trigger the development of pneumonia during aspiration.<sup>18</sup> Although pneumonia caused by infection was excluded from the definition of pulmonary AE in this study, the reporter of AE may misreport pneumonia as pneumonitis. Finally, rebamipide-induced pulmonary AE may have been under-reported because rebamipide is considered not to cause pulmonary AE.

We reviewed individual data on 10 cases of serious pulmonary AE. No serious AE of rebamipide were observed in previous randomized controlled trials.<sup>3</sup> However, in this large population-level study, we did find serious pulmonary AE related to its use. For two of them, the reporter identified afatinib as a suspected drug. The drug label of afatinib contains interstitial lung disease; epidermal growth factor receptor tyrosine kinase inhibitors, including afatinib, have been found to significantly increase the risk of interstitial lung disease in a meta-analysis of AE reported in phase III clinical trials.<sup>19</sup> Two serious cases took cilostazol and HMG-CoA reductase inhibitor, respectively, which reported pulmonary AE during post-marketing use. In addition, due to elder age, comorbidity and multiple co-administered drugs, it is still uncertain that pulmonary AE were caused by rebamipide.

This study shows that pulmonary AE associated with rebamipide use were more frequently reported in elderly patients than in younger adults. This result is consistent with two case studies reporting rebamipide-induced pulmonary AE in the elderly.<sup>5,6</sup> Furthermore, when we assessed the U.S. Food and Drug Administration (FDA) adverse event reporting system database established in September 2020,<sup>20</sup> 29 cases of interstitial lung disease caused by rebamipide were identified. Of these cases, 22 (75.86%) occurred in patients aged 65 years and elder. However, as more pulmonary AE were reported in the elderly for all other A02B drugs, the observed significant correlations between age and rebamipide-related pulmonary AE may have been due to the

presence of lung disorders that are prevalent in elder adults. The vulnerability to rebamipide-induced AE may indeed increase with age, but this result should be interpreted with caution. Nevertheless, the result is important because as society ages the number of elderly patients receiving rebamipide will increase.

This study had some limitations. First, AE were inherently under-reported due to the spontaneous nature of the AE reporting system; therefore, it is difficult to estimate the true incidence of AE accurately. The average incidence of rebamipide-related AE was about 36.1% (range 0%-70%) in the previous studies.<sup>3</sup> Because the input data depend on the reporter, AE may be omitted if the reporter does not consider rebamipide to be the cause of pulmonary AE. This study was unable to determine causality between rebamipide use and pulmonary AE due to the limitations of the database used and the study design. Further studies with sufficient evidence are needed to ascertain whether rebamipide is associated with pulmonary ADR. Second, AE reports in the KIDS-KD do not record information about smoking status. Furthermore, medical history, medication history and indications are not items that must be reported, so they are often omitted. This might have limited the adjustments that can be made due to smoking or underlying diseases, which are important risk factors for pulmonary toxicity of the drug. Last, as mentioned earlier, the reporter might have mistakenly recorded pneumonia as pneumonitis, and vice versa.

Nevertheless, this study has the advantage of examining a large number of rebamipide-AE pairs ( $n = 25\ 918$ ) from the KIDS-KD. To the best of our knowledge, this is the first study to use pharmacovigilance data to analyze pulmonary AE related to rebamipide use.

In conclusion, rebamipide was less frequently reported for pulmonary AE. Although rebamipide is a safe drug, healthcare professionals need to be aware of the potential for rebamipide-induced pulmonary AE in elderly patients.

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## CONFLICT OF INTEREST

The authors had no conflict of interest to declare.

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