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Safety of Gadopiclenol After Its First Year of Clinical Use

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Abstract: Gadopiclenol is a novel, macrocyclic high-relaxivity gadolinium-based contrast agent recently approved for use in magnetic resonance imaging of the central nervous system and body organs at a dose of 0.05 mmol/kg body weight. Postmarketing surveillance of its first year of clinical use in the United States of America showed no serious adverse events (AEs) following over 882,550 administrations and a very low rate of nonserious AEs (1 case every 27,580 exposures). The types of observed AEs were similar to those reported for other gadolinium-based contrast agents in clinical use. Safety data from postmarketing surveillance of gadopiclenol further confirm its positive benefit-risk profile demonstrated in preapproval clinical studies.

Key Words: gadopiclenol, Vueway, Elucirem, gadolinium-based contrast agents, safety, pharmacovigilance, postmarketing surveillance

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The development of a gadolinium-based contrast agent (GBCA) is a highly complex process that scrutinizes every aspect of the new agent in order to provide adequate assurance of its safety at the time of approval.[1] However, clinical development studies are conducted in relatively small patient populations, usually several hundred to several thousand patients, in specific clinical settings. Thus, all possible side effects of a new GBCA cannot be entirely anticipated based on preapproval studies alone.[1–5] Because untoward side effects may be rare, that is, occurring at rates of 1 in 10,000 exposures or lower, they may not be seen in clinical development studies, nor can their actual rates be assessed in a proper manner.[1–5] Therefore, all pharmaceutical companies and national regulatory authorities maintain a system of postmarketing surveillance to identify any untoward side effects that did not appear during preapproval clinical studies, coupled with running risk-management programs to continuously assess the risk-benefit profile of medical imaging or therapeutic products in clinical use to minimize harm.[6–8] The information deriving from postmarketing surveillance and risk-assessment is used by companies and regulatory agencies to update the prescribing information of medical imaging agents and therapeutics, possibly leading to the introduction of new warnings and, less frequently, to a reevaluation of their marketing authorization if the risk-benefit profile is deemed negative. Examples are the warnings and regulatory actions adopted in relation to the possible occurrence of nephrogenic systemic fibrosis (NSF) and retention of gadolinium (Gd) compounds in brain and body tissues following exposure to GBCAs.[9–12]

Gadopiclenol (Elucirem; Guerbet and Vueway; Bracco) is a novel macrocyclic GBCA recently approved at a dose of 0.05 mmol/kg for use in magnetic resonance imaging (MRI) of the central nervous system (CNS) and body organs by the Food and Drug Administration of the United States, the European Commission, following recommendation by the European Medicines Agency, and the regulatory agencies of Switzerland, the United Kingdom, Iceland, Norway, and Liechtenstein. Gadopiclenol is characterized by the highest relaxivity among all the GBCAs in clinical use.[13] Its high r1 relaxivity permits dose lowering without loss of diagnostic information compared with that attainable with higher doses of lower-relaxivity GBCAs.[14] Data from large-scale, preapproval clinical studies revealed a favorable safety profile and noninferior efficacy for 0.05 mmol/kg gadopiclenol when compared intraindividually with gadobutrol (Gadovist/Gadavist; Bayer Healthcare) at twice the dose (0.1 mmol/kg).[15–17]

"Adverse events" (AEs) are defined by all regulatory authorities as any untoward medical occurrence associated with the use of a medicinal product used to treat or diagnose disease in humans, whether or not considered product related, whereas "adverse reactions" (ARs) are defined as those AEs for which a causal relationship between exposure to a medicinal product and an untoward medical occurrence is at least a reasonable possibility.[18] The 2 terms are often used interchangeably[19]; however, ARs represent only a fraction of the AEs that occur following exposure to a medicinal product, meaning that reporting rates of AEs are higher than those of ARs. Independently of a possible causal relationship, herein we summarize the type, seriousness, and frequency of AEs observed during the first year of postapproval use of gadopiclenol, which occurred in the United States from February 1, 2023 to March 20, 2024.

METHODS

Data Collection

In compliance with Good Pharmacovigilance Practices and the most stringent legislative regulations,[20–22] both Bracco and Guerbet maintain their own pharmacovigilance (PV) systems, consisting of a dedicated organizational structure, with a network of qualified and trained personnel, standard operating procedures, working guides and processes, dedicated computerized systems and databases, and quality control systems. The PV systems of the 2 companies monitor the safety of every product the companies market around the world across their entire clinical use in healthcare practices. Data are collected from all available sources, for example, case reports spontaneously reported to health authorities and/or directly to the companies, medical and scientific literature, social media, databases maintained by regulatory agencies, clinical and epidemiological studies, and administrative and claims data from health insurers. All the AEs that were reported through these different sources to have occurred after exposure to gadopiclenol were therefore properly collected and recorded into the PV databases maintained by the 2 companies.

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Data Extraction

All available information obtained from postmarketing surveillance of the clinical use of gadopiclenol in the United States, including number of patients experiencing AEs, demographic data, MRI indications, and individual symptoms, were extracted from the PV databases. Symptoms were coded using system organ classes and preferred terms according to the latest standard medical terminology for PV taken from the Medical Dictionary for Regulatory Activities (MedDRA), which is provided and regularly updated by the International Conference of Harmonization.[23]

Adverse Event Classification

All the AEs observed after exposure to gadopiclenol were classified as "serious" or "nonserious" by qualified personnel according to the definition provided by health authorities,[24] that is, an AE is considered "serious" when (i) it has a fatal outcome; (ii) it is life-threatening; (iii) it results in hospitalization, or in a prolongation of hospitalization; (iv) it results in disability or permanent damage; (v) it causes a congenital anomaly or birth defect; (vi) it requires intervention to prevent permanent impairment or damage; and (vii) it does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent 1 of the other outcomes. Nonserious AEs are those associated with the use of a medical product, which do not meet any of the criteria for serious AEs.

Estimate of Reporting Rates

The number of patients experiencing AEs between February 1, 2023 and March 20, 2024 was used as the numerator. Because dosing of all medical imaging agents mostly occurs as a single administration, in the reporting of periodic safety updates to health authorities, patient exposure is usually estimated based on the number of sales units sold within a given period. Therefore, the number of Elucirem and Vueway units sold between February 1, 2023 and March 20, 2024 was used as the denominator to calculate reporting rates of gadopiclenol AEs during this specific timeframe. Reporting rates were calculated as the number of patients experiencing AEs during this period or the number of symptoms divided by the estimated number of exposures (and then multiplied by 100 for percentages). Only the number of gadopiclenol units sold in the United States were considered for this analysis, as it was the sole country where gadopiclenol was marketed during the reporting timeframe.

RESULTS

Over an estimated exposure of 882,550 patients, no serious AEs were observed in the first year of postapproval use of gadopiclenol in routine radiological practice in the United States. A total of 32 patients experienced nonserious AEs, with an overall reporting rate of 1 case every 27,580 exposures to the GBCA (0.0036%). All reported AEs occurred in adult patients. Time of onset of the AEs was not always reported. When reported, it was always within the first minutes following the administration of gadopiclenol, and most of the AEs resolved without the need for specific medical intervention. The majority of patients were female (56.25%) and below 65 years of age (78.9%) when this information was available. The main indications for the contrast-enhanced MR examination, when available, were MRI of the CNS (61.5%), abdomen (31.4%), and breast (7.1%). The list of the reported symptoms and reporting rates is presented in Table 1. Overall, 51 symptoms were reported for the 32 nonserious AE cases, the most common of which were gastrointestinal disorders (nausea, retching, and/or vomiting), with nausea experienced every 126,079 administrations and vomiting every 110,319 administrations. Dizziness was reported by 4 patients (1 case every 220,638 administrations). The MedDRA preferred terms related to hypersensitivity AEs were hypersensitivity (4 reports), urticaria (7 reports), pruritus (3 reports), sneezing (2 reports), and single reports of dyspnea, throat tightness, pharyngeal swelling, erythema, erythematous rash, and macular rash. All the reported hypersensitivity AE cases were nonserious, were associated with 1 or more related symptoms, and their overall rate was below 1 case every 100,000 exposures.

TABLE 1. Symptoms Reported in 32 Adverse Event Cases by MedDRA System Organ Class and Preferred Terms From Postmarketing Sources for Gadopiclenol (Exposure: 882,550 From February 1, 2023 to March 20, 2024)

Symptoms by MedDRA System Organ Class (SOC) and Preferred Term	No. by Seriousness		Reporting Rate %*
	Serious	Nonserious	
Eye disorders			
Vision blurred	0	1	0.00011%
Gastrointestinal disorders			
Nausea	0	7	0.00079%
Retching	0	1	0.00011%
Vomiting	0	8	0.00091%
General disorders and administration site conditions			
Drug ineffective	0	1	0.00011%
Swelling face	0	1	0.00011%
Immune system disorders			
Hypersensitivity	0	4	0.00045%
Musculoskeletal and connective tissue disorders			
Muscle twitching	0	1	0.00011%
Nervous system disorders			
Dizziness	0	4	0.00045%
Dysgeusia	0	1	0.00011%
Hypoaesthesia	0	1	0.00011%
Paraesthesia	0	1	0.00011%
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	0	1	0.00011%
Pharyngeal swelling	0	1	0.00011%
Sneezing	0	2	0.00023%
Throat tightness	0	1	0.00011%
Skin and subcutaneous tissue disorders			
Erythema	0	1	0.00011%
Pruritus	0	3	0.00034%
Rash erythematous	0	1	0.00011%
Rash macular	0	1	0.00011%
Urticaria	0	7	0.00079%
Vascular disorders			
Flushing	0	2	0.00023%
Total no. symptoms	**0**	**51**	
Total no. serious AE cases	**0/882,550 exposures**		
Total no. nonserious AE cases	**32/882,550 exposures (0.0036%)**		

*Reporting rate %: no. symptoms/882,550 × 100.

DISCUSSION

AEs are known to occur following the administration of all medical products, medical imaging agents included, as reported in their approved prescribing information. Acute AEs are defined as those that occur within the first 60 minutes following exposure to the medical imaging agent.[25] As per the American College of Radiology Contrast Media Manual, rates of acute ARs to GBCAs administered intravenously at approved clinical doses range from 0.07% to 2.4%.[26] The severity of ARs to GBCAs can range from nonserious and mild in intensity, that

TABLE 2. Categories of Acute Reactions to Gadolinium-Based Contrast Agents (Adapted From American College of Radiology[26])

Mild (self-limited, nonprogressive)	
Altered taste	Headache, dizziness
Pallor, flushing, warmth, chills, sweats	Mild and transient nausea/vomiting
Scattered and/or transient urticaria/itching	Mild and transient hypertension or hypotension
Cough	Short-lasting and self-limited vasovagal reaction
Nasal congestion, rhinorrhea, sneezing, conjunctivitis	Mild and limited tachycardia/bradycardia
Moderate (requires medical treatment, may progress if untreated)	
Protracted nausea/vomiting	Moderate and protracted tachycardia
Diffuse urticaria/itching	Hypertension/hypotension/vasovagal reaction that requires and responds to treatment
Diffuse erythema, stable vital signs	
Bronchospasm, dyspnea	Isolated chest pain, no electrocardiographic changes
Facial/laryngeal edema without dyspnea	
Severe (life-threatening, may result in inpatient hospitalization, prolongation of hospitalization, permanent morbidity or death)	
Hypotensive shock	Severe or rapidly progressing laryngeal edema with stridor and/or hypoxia
Respiratory arrest	Severe bronchospasm with significant hypoxia
Cardiac arrest	Diffuse erythema with hypotension
Vasovagal reaction resistant to treatment	Hypertensive emergency
Convulsions/seizures	Clinically manifested arrhythmias
Unresponsiveness	

is, transient and self-resolving symptoms, to serious life-threatening events, as shown in Table 2.[26] Most acute ARs to GBCAs are mild, including nausea, vomiting, headache, dizziness, and injection site reactions.[26] Serious ARs, such as anaphylactic or anaphylactic-like events, occur rarely (less than 1 in every 10,000 administered doses).[26] Use of some GBCAs has also been associated with the late occurrence of NSF, a rare, serious, progressive systemic fibrosing disorder in patients with severe renal insufficiency. The possible development of this serious, late complication has been largely eliminated with the use of GBCAs considered to be of lower risk.[27] Potential safety concerns have also been raised by reports of retention of chemical forms of Gd in human tissues even in patients with normal renal function. To date, however, there is no evidence of any adverse biological or clinical effects from long-term Gd retention in patients exposed to GBCAs.[27,28]

Gadopiclenol is the most recently approved macrocyclic GBCA, indicated for use in MRI of the CNS and body organs in adults and pediatric patients of 2 years of age and older. Due to its high relaxivity and contrast enhancement efficacy, it is approved at a lower dose than the approved doses of other commercially available GBCAs of the same class. No serious AEs were observed during the first year of its clinical use, across an estimated 882,550 intravenous administrations (Table 1). Likewise, there were no reports of NSF or Gd retention. The rate of acute, nonserious AEs was extremely low, that is, 1 case every 27,580 estimated exposures (0.0036%, Table 1). Hypersensitivity AE cases occurred in less than every 100,000 exposures. Neither company received reports of AEs following off-label use of the product. Most of the reported nonserious AE cases resolved without the need of any treatment. The type of symptoms observed in the reported AE cases (Table 1) was similar to that reported for other GBCAs in clinical use.[26,29–34]

The AE reporting rate following administration of gadopiclenol was extremely low, lower than that reported in the postmarketing surveillance of other GBCAs.[29–34] Specifically, when compared with the most recent postmarketing surveillance data for gadobutrol[30] and gadoterate meglumine,[31] the AE reporting rate for gadopiclenol was roughly half that of gadoterate meglumine and one tenth that of gadobutrol (Table 3). To note is that the most recent postmarketing surveillance data for gadobutrol[30] and gadoterate meglumine[31] covered extended periods of more than 25 years, whereas the postmarketing reporting period for gadopiclenol covers only the first year of clinical use. Thus, surveillance of gadobutrol and gadoterate meglumine included both the initial postlaunch period and an extended period of market maturity, whereas the current report for gadopiclenol covers only the initial period of clinical use. Typically, there is increased reporting of AEs in the first months/years after launch of a new drug compared with later in the product life cycle. This effect, termed "the Weber effect",[35] reflects initial increased reporting of AEs due to unfamiliarity and uncertainty with a new product, which later declines when practitioners become familiar and more confident with the new product. It may also reflect increased nervousness or anxiety on the part of practitioners, which in turn increases patient anxiety and susceptibility to certain types of AE, an effect termed "the Lalli effect."[36] Both the Weber and Lalli effects have been reported in routine radiological practice, with radiologists experiencing an increased incidence of AEs for a shorter or longer period after switching from one medical imaging agent to another, even within the same class of agents.[36] In postmarketing surveillance of GBCAs, Knopp et al[33] reported an early rate of 0.016% for the first approved GBCA, gadopentetate dimeglumine, which declined to 0.002% in an assessment of ARs after 45 million administrations.

TABLE 3. Comparison of AE Reporting Rates From Postmarketing Surveillance of Gadopiclenol With AE Rates Reported From Postmarketing Surveillance of Other Macrocyclic GBCAs

GBCA	Period	No. Patients Reporting AEs	No. Exposures	AE Reporting Rate
Gadopiclenol (this study)	02/2023–03/2024	32	882,550	0.0036%
Gadobutrol (Endrikat et al[30])	02/1998–12/2022	37,840	106,100,000	0.0356%
Gadoterate meglumine (de Kerviler et al[31])	03/1989–09/2014	3797	50,822,289	0.0075%

Likewise, Matsumura et al,[34] also with gadopentetate dimeglumine, recorded a decline from 0.021% to 0.014%. More recently, Endrikat et al[29] reported higher AR rates in the early years after the introduction of gadobutrol followed by a trend toward lower rates over time. A retrospective study carried out by Davenport et al[37] reported an increased rate of acute allergic-like AEs following the substitution of gadobenate dimeglumine for gadopentetate dimeglumine due to the risk of NSF with the latter agent. Subsequent AE rates with gadobenate dimeglumine were not significantly different from the original baseline reaction rate with gadopentetate dimeglumine.[37] Likewise, a trend toward a decrease in the rate of AEs following exposure to gadobenate dimeglumine was also reported by Fakhran et al[38] over 7.5 years of a prospective observational study of the safety of the agent, with the authors concluding that their findings were consistent with the Weber and Lalli effects.[39] The AE reporting rate observed for gadopiclenol in the first year of clinical use in the United States was already so low that it is difficult to imply a Weber or Lalli effect, and it remains to be seen whether a decline in the reporting rate will occur with more extended clinical use in more countries.

CONCLUSIONS

During its first year of clinical use in the United States, gadopiclenol has shown a good safety profile. No serious AEs were reported, and a very low rate of nonserious AEs was observed. The safety data from postmarketing surveillance of this novel macrocyclic, high-relaxivity GBCA further confirm the positive benefit-risk profile demonstrated in preapproval clinical studies. Further evaluation of postmarketing safety of gadopiclenol is warranted following exposure to larger numbers of patients across different geographies.

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