This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Report on the Investigation Results

November 11, 2017
Pharmaceuticals and Medical Devices Agency

I. Overview of drug

[Non-proprietary name]	See Attachment 1
[Brand name]	See Attachment 1
[Approval holder]	See Attachment 1
[Indications]	See Attachment 1
[Dosage and administration]	See Attachment 1
[Remarks]	Nothing in particular
[Investigating office]	Office of Safety II

II. Gadolinium-based contrast agents

Gadolinium-based contrast agents (GBCAs) are the chelating compounds containing paramagnetic metal gadolinium (Gd) of the rare earth elements with the effect to shorten T1 (longitudinal relaxation time) and T2 (transverse relaxation time) of the hydrogen nuclei in magnetic resonance imaging (MRI), and currently 6 products are available in Japan (See Attachment 1). GBCAs are classified into linear agents with a linear structure and macrocyclic agents with a macrocyclic structure based on their chelate structures: The linear agents include gadodiamide hydrate, meglumine gadopentetate and gadoxetate sodium while the macrocyclic agents include gadoteridol, meglumine gadoterate and gadobutrol. All products are administered intravenously. Gadoxetate sodium is indicated for “contrast imaging of hepatic tumors”, and 5 other products are indicated for contrast imaging of brain/spinal cord, and trunk/extremities” (Table 1)

Table 1 Structure and indications of GBCAs

Structure	Linear			Macrocyclic		
Non-proprietary name	Gadodiamide hydrate	Meglumine gadopentetate	Gadoxetate sodium	Gadoteridol	Meglumine gadoterate	Gadobutrol
Indications	Following contrast imaging in MRI Contrast imaging of brain and spinal cord Contrast imaging of trunk and extremities		Contrast imaging in MRI of hepatic tumor	Following contrast imaging in MRI Contrast imaging of brain and spinal cord Contrast imaging of trunk and extremities		

III. Background of this investigation

Since 2014, there have been a number of reports that Gd remains in the brain tissues of some patients who underwent several contrast MRI scans, long after the last administration of a GBCA. The U.S. Food and Drug Administration (FDA) released Drug Safety Communications related to GBCAs on July 27, 2015 based on these reports alerting the health care professionals to consider limiting use of GBCAs to clinical circumstances in which additional information provided by contrast imaging is necessary and reassessing the necessity of repetitive MRI scans with GBCAs in established treatment protocols, although it is still unknown whether these Gd deposits are harmful or can lead to adverse health effects[1]. The National Center for Toxicological Research, FDA has started its study of this possible safety risk due to Gd retention in the brain tissues. Moreover in 2016, the U.S. National Institutes of Health has shown the guideline that administration of GBCAs should be limited to cases of clinical necessity or when specified by Institutional Review Board approved protocols, as well as consideration of using a macrocyclic GBCA when a GBCA is deemed necessary[2]. Also, the FDA announced that they have not identified evidence that Gd retention in the brain is harmful and they will continue to assess the safety of GBCAs in the Drug Safety Communications issued on May 22, 2017[3]. On September 8, 2017, an Advisory Committee held by the FDA has determined to request additional studies on Gd retention to manufacturers and that package inserts of the products should be revised to include a warning about Gd retention in the brain and other body organs.

Meanwhile in the EU, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) reviewed Gd deposition in the brain tissues, and recommended that the marketing authorizations of some linear GBCAs should be suspended in its assessment report published on March 10, 2017 and reassessment report published on July 7, 2017[4]. The subsequent Committee for Medicinal Products for Human

[1] FDA HP: FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) (https://www.fda.gov/downloads/Drugs/DrugSafety/UCM455390.pdf)
[2] Malayeri, AA, et al. National Institutes of Health Perspective on Reports of Gadolinium Deposition in the Brain, J. Am. Col Radio. 2016; 13: 237-241
[3] FDA HP: FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue (https://www.fda.gov/downloads/Drugs/DrugSafety/UCM559654.pdf)
[4] EMA HP: PRAC confirms restrictions on the use of linear gadolinium agents (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500230928.pdf)

Use (CHMP) held on July 21, 2017 announced that they follow the PRAC recommendations as the EMA's final opinions[5], and the final recommendations have been sent to the European Commission. Similar to the U.S., these measures are based on the reports on Gd retention in the brain tissues by use of GBCAs, and the following measures have been shown since benefit-risk ratio differs depending on the structure and indication of the GBCAs.

- Marketing authorization of some linear GBCAs should be suspended.
- Among the linear GBCAs, those indicated for use in liver and intraarticular contrast imaging only (including agents with pending indication restrictions) are taken into the liver and meet an important diagnostic need and the dose of Gd used for joint injection is very low[5]. Therefore, marketing authorization of these products may be maintained, subject to revision of the package inserts[6].
  Among products in the Japanese market, gadoxetate sodium falls among the linear GBCAs subject to revision of package inserts. Major revisions are as follows.
  - Therapeutic indications: Description that gadoxetate sodium should be used only when diagnostic information by the drug and late-phase imaging are required but non-contrast MRI scan is not applicable should be added.
  - Posology and method of administration: Description that gadoxetate sodium should only be used at the lowest therapeutic dose for diagnosis should be added.
  - Special warnings and precautions for use: Descriptions that Gd can be retained in the brain and other tissues of the body after administration of gadoxetate sodium and T1-weighted signal intensity in the brain can be increased dose-dependently; that its clinical consequences are unknown; and that diagnostic benefits of the patients who require repetitive use of GBCAs should be assessed based on the Gd retention in the brain and other tissues should be added.
  - Pharmacokinetic properties: Descriptions that gadoxetate sodium is a linear GBCA for which it has been reported that T1-weighted signal intensity is increased in the dentate nucleus, globus pallidus, and thalamus dose-dependently should be added.
- Marketing authorization of macrocyclic GBCAs will be maintained subject to revision of the package inserts[5].
  Among products in the Japanese market, gadoteridol, meglumine gadoterate, and gadobutrol fall among the macrocyclic GBCAs of which revision of the package inserts is deemed necessary. Major revisions are as follows.
  - Therapeutic indications: Description that gadoteridol, meglumine gadoterate, and gadobutrol should be used only when diagnostic information by macrocyclic GBCAs is essential should be added.
  - Posology and method of administration: Description that gadoteridol, meglumine gadoterate, and gadobutrol should only be used at the lowest therapeutic dose for diagnosis should be added.

[5] EMA HP: EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500231824.pdf)
[6] EMA HP: Product Information as approved by the CHMP on 20 July 2017, pending endorsement by the European Commission (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500231823.pdf)

There has been no clear evidence that retention of GBCAs are harmful, and the recommendation for suspension of marketing authorization has been announced as a precautionary measure.

In Japan, there is no description of the information on Gd retention in the brain tissues in the current package inserts of all GBCAs listed in Attachment 1. Information on the related literature has been collected while opinions from the related academic societies have been heard regarding the necessity of providing information to the clinical practices. In light of the above situations in other countries as well, the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (MHLW) requested the Pharmaceuticals and Medical Devices Agency (PMDA) to conduct an investigation regarding the safety of GBCAs on August 24, 2017. In response to the request, PMDA has investigated Gd retention in the brain tissues by use of GBCAs and considered the measures to be taken in Japan.

The PMDA has held an Expert Discussion as part of the investigation. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the products, in accordance with the provisions of “Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20/8 dated December 25, 2008).

IV.Investigation by PMDA

1. Literature information related to Gd retention in the brain tissues

Among the published literature reported to the PMDA from marketing authorization holders (MAHs) by August 31, 2017, 74 literatures related to Gd retention in the brain tissues by use of GBCAs were reviewed and the major contents are as follows. The summary of all literature reviewed is shown in Attachment 2.

(1) Non-clinical studies

1) Signal intensity in T1-weighted MR images

(i) The repeated intravenous dose corresponding to 4-fold the clinical dose per body surface area 2.5 mmol/kg of a linear GBCA gadodiamide hydrate, meglumine gadopentetate or dimeglumine gadobenate (unapproved in Japan), or a macrocyclic GBCA meglumine gadoterate or gadobutrol was administered to rats (10 rats per group) 5days weekly for 2 weeks, respectively. Repeated intravenous dose of saline was administered to the control group. The signal intensity ratios of the deep cerebellar nuclei/pons and globus pallidus/thalamus were observed 3 and 24 days after the last dose. The signal intensity ratio of the deep cerebellar nuclei/pons increased in the linear GBCA groups compared to the baseline (gadodiamide hydrate: 3 days after last dose P <0.01, t-test, 24 days after last dose p <0.01: t-test; dimeglumine gadobenate: 3 days after last dose P <0.01: t-test, 24 days after last dose P <0.05: t-test), while there was no significant increase in the meglumine gadopentetate group. No change was observed in the

macrocyclic GBCA groups. There was no change in the signal intensity ratio of the globus pallidus/thalamus in all treatment groups[7].

2) Signal intensity in T1-weighted MR images and Gd-concentration in the brain

(ii) The repeated intravenous dose which is considered equivalent to the clinical dose 0.6 mmol/kg of a linear GBCA gadodiamide hydrate or a macrocyclic GBCA meglumine gadoterate was administered to rats (7 rats per group) 4 days weekly for 5 weeks, respectively. Repeated intravenous dose of saline was administered to the control group. On the 12th administration, the signal intensity ratio of the deep cerebellar nuclei/ cerebellar cortex in the gadodiamide hydrate group was significantly higher (mean ± SD) (1.070 ± 0.024) than the meglumine gadoterate group (1.000 ± 0.033, P <0.001: ANOVA test) and the control group (1.019 ± 0.22, P <0.001: ANOVA test) which did not decrease 5 weeks after the last dose. Total Gd concentration in the cerebellum measured by inductively coupled plasma-mass spectrometry 5 weeks after the last dose was significantly higher in the gadodiamide hydrate group (3.66 ± 0.91 nmol/g) than the meglumine gadoterate group (0.26 ± 0.12 nmol/g, P <0.05: Kruskal-Wallis test) and the control group (0.06 ± 0.10 nmol/g, P <0.05: Kruskal-Wallis test)[8].

(iii) The repeated intravenous dose of 0.6 mmol/kg of a linear GBCA meglumine gadopentetate, gadodiamide hydrate or dimeglumine gadobenate, or a macrocyclic GBCA meglumine gadoterate was administered to rats (8 rats per group) 4 days weekly for 5 weeks, respectively. Repeated intravenous dose of saline was administered to the control group. Four weeks after the last dose, high signal intensity in the deep cerebellar nuclei was observed in the linear GBCA groups, and the signal intensity ratio of the deep cerebellar nuclei/cerebellar cortex was significantly higher in the gadodiamide hydrate group (P = 0.003: ANOVA test) and the meglumine gadopentetate group (P = 0.007: ANOVA test) than the control group. Compared to the control group, the increase of the signal intensity ratio in the dimeglumine gadobenate group was not significant (P = 0.06: ANOVA test), and there was no significant difference in the meglumine gadoterate group (P = 0.78: ANOVA test). Total Gd concentration in the cerebellum measured by inductively coupled plasma-mass spectrometry 4 weeks after the last dose (mean ± SD) was significantly higher in the linear GBCAs, the gadodiamide hydrate group (3.75 ± 0.18 nmol/g), meglumine gadopentetate group (1.67 ± 0.17 nmol/g) and the dimeglumine gadobenate group (1.21 ± 0.48 nmol/g) than the control group (0.09 ± 0.12 nmol/g). Furthermore, the gadodiamide hydrate, meglumine gadopentetate, and dimeglumine gadobenate groups were significantly

[7] Jost G et al. Signal Increase on Unenhanced T1-Weighted Images in the Rat Brain After Repeated, Extended Doses of Gadolinium-Based Contrast Agents: Comparison of Linear and Macrocyclic Agents. Invest Radiol. Invest Radiol. 2016: 51; 83-89

[8] Robert P et al. T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats: Difference Between Linear and Macrocyclic Agents. Invest Radiol. 2015; 50: 473-480

greater compared to the macrocyclic GBCA meglumine gadoterate group (0.27 ± 0.16 nmol/g)[9].

(iv) The repeated intravenous dose of 2.5 mmol/kg of a linear GBCA gadodiamide hydrate or dimeglumine gadobenate, or a macrocyclic GBCA gadobutrol or gadoteridol was administered to rats (6 rats per group) 5 days weekly for 4 weeks, respectively. Repeated intravenous dose of saline was administered to the control group. The rate of change of the signal intensity in the dentate nucleus between baseline and 3 days after the last dose of a contrast agent showed significant increase in the GBCA groups compared to the saline group. An examination of Gd concentration on 7 days after the last dose by inductively coupled plasma-mass spectrometry found Gd retention in the brain in all GBCA groups (gadodiamide hydrate mean 6.9 μg/g [95% confidence interval (CI]); 6.2-7.0 μg/g), dimeglumine gadobenate 4.7 μg/g (95%CI; 3.5-6.1 μg/g), gadobutrol 1.6 μg/g (95%CI; 0.9-4.7 μg/g), gadoteridol 0 μg/g (95%CI; 0-0.2 μg/g))[10].

3) Gd concentration in the brain

(v) The repeated intravenous dose of 2.5 mmol/kg of a linear GBCA meglumine gadopentetate or gadodiamide hydrate, or a macrocyclic GBCA gadobutrol or gadoteridol was administered to rats (10 rats per group) 5days weekly for 4weeks, respectively. Repeated intravenous dose of saline was administered to the control group. As a result of examination of Gd concentration 8 weeks 8 after the last dose by inductively coupled plasma-mass spectrometry, Gd concentration in the brain (mean ± SD) was higher in the linear GBCA groups than the macrocyclic GBCA groups (meglumine gadopentetate : 13.1 ± 7.3 nmol/g, gadodiamide hydrate: 11.1 ± 5.1 nmol/g, gadobutrol 0.7 ± 0.4 nmol/g, gadoteridol: 0.5 ± 0.2 nmol/g). There was no histological change in the brain in any of the GBCA groups[11].

(2) Clinical studies

1) Signal intensity on enhanced T1-weighted MR images with linear GBCAs

(vi) In the study of 19 patients who underwent enhanced MRI scans with gadodiamide hydrate or meglumine gadopentetate for 6 to 12 times and 16 patients who underwent unenhanced MRI scans for 6 times or more to compare their unenhanced T1-weighted MR images, the signal intensity ratios of the dentate nucleus/pons and globus pallidus/thalamus were significantly higher in the group with a history of GBCAs than the group without a history of GBCAs (both P <0.001: t-test)[12].

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[9] Robert P et al. Linear Gadolinium-Based Contrast Agents Are Associated With Brain Gadolinium Retention in Healthy Rats. Invest Radiol. 2016; 51: 73-82

[10] McDonald, R.J et al. Comparison of Gadolinium Concentrations within Multiple Rat Organs after Intravenous Administration of Linear versus Macrocyclic Gadolinium Chelates. Radiology.2017; 161594 [Epub ahead of print]

[11] Lohrke J et al. Histology and Gadolinium Distribution in the Rodent Brain After the Administration of Cumulative High Doses of Linear and Macrocyclic Gadolinium-Based Contrast Agents. Invest Radiol. Invest Radiol. 2017; 52: 324-333

[12] Kanda T et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology. 2014; 270: 834-841

(vii) The effects of administration of gadoxetate sodium and gadodiamide hydrate on agent-induced high signal intensity of the dentate nucleus in unenhanced T1-weighted MR images were examined in 33 patients who received gadoxetate sodium for 5 times or more, 33 patients who received gadoxetate sodium only once, 33 patients who received gadodiamide hydrate for 5 times or more, and 33 patients without a history of GBCAs. As a result, the signal intensity ratio of the dentate nucleus/pons was significantly higher in the gadodiamide hydrate group (<0.0001: Dunn test) while there was no significant difference in the gadoxetate sodium groups who received 5 times or more and only once (P = 0.3912 and P = 1.0000, respectively: Dunn test) compared to the group without a history of GBCAs. While there was a correlation between the signal intensity ratio of the dentate nucleus/pons and the number of doses in the gadodiamide hydrate group, there was no correlation in the gadoxetate sodium group[13].

2) Signal intensity on enhanced T1-weighted MR images with macrocyclic GBCAs

(viii) Thirty-three patients who received meglumine gadoterate or gadobutrol for 20 times or more in total (mean number of doses: 23.03 times) were examined. The mean interval between first and last MR imaging examination was 273.06 weeks, and the mean dose intervals was 12.09 weeks. Signal intensity ratio differences in unenhanced T1-weighted images were (dentate nucleus/pons: P = 0.248: t-test, dentate nucleus/middle cerebellar peduncle: P = 0.521: t-test)[14].

(ix) Measurement of the signal intensity in unenhanced T1-weighted images of the dentate nucleus, pons, substantia nigra, thalamus and globus pallidus in 24 children (aged 5 to 18 years) who received meglumine gadoterate or gadoteridol for 9 times or more (mean number of doses: 14.21 times) and 24 patients matched for age and sex who underwent unenhanced MRI scans showed no significant difference in the signal intensity of each brain section in the group with a history of GBCAs compared to the group without a history of GBCAs (dentate nucleus P = 0.75, pons P = 0.66, substantia nigra P = 0.52, globus pallidus P = 0.69, thalamus P = 0.42: t-test), and there was no difference in the signal intensity ratios of dentate nucleus/pons and globus pallidus/thalamus (dentate nucleus/pons P = 0.37, globus pallidus/thalamus P = 0.29: t-test)[15].

(x) Signal intensity on unenhanced T1-weighted images of the globus pallidus and dentate nucleus of 50 children (aged 2 to 18 years) who received

[13] Ichikawa S et al. Contrast Agent-Induced High Signal Intensity in Dentate Nucleus on Unenhanced T1-Weighted Images: Comparison of Gadodiamide and Gadoxetic Acid. Invest Radiol. 2017; 52: 389-395
[14] Radbruch A et al. No Signal Intensity Increase in the Dentate Nucleus on Unenhanced T1-weighted MR Images after More than 20 Serial Injections of Macrocyclic Gadolinium-based Contrast Agents. Radiology. 2017; 282: 699-707
[15] Tibussek D et al. Gadolinium Brain Deposition after Macrocyclic Gadolinium Administration: A Pediatric Case-Control Study. Radiology 2017; 285: 223-230.

meglumine gadoterate for 6 times or more (6 to 18 times) and a control group of 59 age-matched GBCA-naïve patients who underwent unenhanced MRI scans was evaluated. The signal intensity ratios of the globus pallidus/thalamus and dentate nucleus/pons were significantly correlated with the number of doses of GBCAs (P = 0.002 and P = 0.021, respectively: F-test), and calculation of the signal intensity ratios of the globus pallidus/thalamus and dentate nucleus/pons on unenhanced T1-weighted images at the initial and the last scans showed significant differences (P = 0.004 and P = 0.001, respectively: t-test). However, no high signal intensity in the globus pallidus or dentate nucleus was visually confirmed[16].

3) Comparison of signal intensity on enhanced T1-weighted MR images with linear and macrocyclic GBCAs

(xi) Fifty patients, respectively, who received a linear GBCA meglumine gadopentetate alone and who received a macrocyclic GBCA meglumine gadoterate alone for at least 6 times were analyzed. The mean values of dose intervals in the linear Gd-based contrast group and the macrocyclic GBCA group were 14.00 weeks and 11.28 weeks, respectively. The mean values of number of doses were 7.32 times and 7.06 times, respectively. The signal intensity ratio difference between the last and first imaging for the dentate nucleus/pons on unenhanced T1-weighted images (mean ± SD) was significantly greater in the linear agent (dentate nucleus: 0.0407 ± 0.0398, P <0.001: t-test; globus pallidus: 0.0287 ± 0.0275, P <0.001: t-test) and there was no significant difference in the macrocyclic agent (dentate nucleus: 0.0016 ± 0.0266, P = 0.680: t-test; globus pallidus: 0.0031 ± 0.0354, P = 0.538: t-test)[17].

4) Gd concentration in the brain

(xii) Gd concentration in the brain tissues of 5 autopsy cases who received a linear GBCA gadodiamide hydrate or meglumine gadopentetate in a cumulative total of twice or more and 5 autopsy cases without a history of GBCAs was measured by inductively coupled plasma-mass spectrometry. Two of the 5 cases had received a macrocyclic GBCA gadoteridol once. The interval between the last dose and autopsy was 0.5 to 39 months in the GBCA group. Gd was detected in brain tissue specimens of all patients who received a GBCA (mean 0.25 ± SD 0.44 μg/g), and the Gd concentration in the brain (mean ± SD) was significantly higher than the group without a history of GBCAs (0.0025 ± 0.005 μg/g) (P = 0.004: Fisher permutation test). The mean Gd concentrations in the dentate nucleus and globus pallidus (0.44 ± 0.63 μg/g) were significantly higher than those in the cerebellar cortex,

[16] Rossi Espagnet MC et al. Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children. Pediatr Radiol. 2017; 47: 1345–1352

[17] Radbruch A et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology. 2015; 275: 783-791

frontal cortex and frontal white matter (0.12 ± 0.16 μg /g) (P = 0.029: Fisher permutation test)[18].

(xiii) Gd concentration in the brain tissue was measured by inductively coupled plasma-mass spectrometry in 9 autopsy cases who received one of the linear GBCAs gadoxetate sodium or dimeglumine gadobenate, or the macrocyclic GBCAs gadoteridol or gadobutrol for 1 to 11 times and 9 autopsy cases without a history of enhanced MRI scan. The interval between the last dose of GBCA and autopsy was 5 to 392 days. In all autopsy cases who received a GBCA, Gd retention was confirmed in brain sections such as dentate nucleus or globus pallidus [gadoxetate sodium (1 case) (dentate nucleus: not measured, globus pallidus: 0.148 μg /g); dimeglumine gadobenate (1 case) (dentate nucleus: 0.078 μg/g, globus pallidus: 0.052 μg /g); gadoteridol (5 cases) (dentate nucleus: <0.004 μg/g-0.078 μg/g (minimum-maximum, the same applies below), globus pallidus: <0.005 μg/g-0.066 μg/g), gadobutrol (2 cases) (dentate nucleus: 0.111-1.070 μg/g, globus pallidus: 0.188-0.625 μg/g)][19].

2. Accumulation of case reports in Japan

The Japanese cases whose events possibly related to Gd retention in the brain tissues (excluding the cases for which Gd retention in the brain tissues was not confirmed from the clinical course found by autopsy or on MR images) in the information on patients who received GBCAs reported to the PMDA by Japanese MAHs of GBCAs between the initial marketing and August 31, 2017[20] included 2 cases (2 events) of gadodiamide hydrate, 6 cases (7 events) of meglumine gadopentetate, 2 cases (2 events) of gadoteridol, and 1 case (2 events) of meglumine gadoterate. The reported events as termed according to the Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA-PT) included 6 events of “contrast media deposition”, 4 events of “nuclear magnetic resonance imaging brain abnormal”, 1 events of “hyperintensity in brain deep nuclei”, 1 event of “nuclear magnetic resonance imaging abnormal”, and 1 event of “medication residue present”, and the number of events per product was as shown in Table 2. There was no occurrence of clinical symptoms in all Japanese cases reported as related to Gd retention in the brain tissues.

Table 2 Events related to Gd retention in the brain tissue (number of events)

MedDRA-PT	Linear			Macrocyclic		
	Gadodiamide hydrate	Meglumine gadopentetate	Gadoxetate sodium	Gadoteridol	Meglumine gadoterate	Gadobutrol

[18] Kanda T et al. Gadolinium-based Contrast Agent Accumulates in the Brain Even in Subjects without Severe Renal Dysfunction: Evaluation of Autopsy Brain Specimens with Inductively Coupled Plasma Mass Spectroscopy. Radiology. 2015; 276: 228-232

[19] Murata N et al. Macrocyclic and Other Non-Group 1 Gadolinium Contrast Agents Deposit Low Levels of Gadolinium in Brain and Bone Tissue: Preliminary Results From 9 Patients With Normal Renal Function. Invest Radiol. 2016; 51: 447-453

[20] Events corresponding to “nuclear magnetic resonance imaging abnormal”, “nuclear magnetic resonance imaging brain abnormal”, “biopsy brain abnormal”, “medication residue present”, “gadolinium deposition disease”, “contrast media deposition”, “hyperintensity in brain deep nuclei”, “drug clearance decreased” and “metal poisoning” in MedDRA-PT

Contrast media deposition	0	6	0	0	0	0
Nuclear magnetic resonance imaging brain abnormal	2	0	0	1	1	0
Hyperintensity in brain deep nuclei	0	1	0	0	0	0
Nuclear magnetic resonance imaging abnormal	0	0	0	1	0	0
Medication residue present	0	0	0	0	1	0

3. Accumulation of case reports in other countries

The foreign cases whose events possibly related to Gd retention in the brain tissues (excluding the cases for which Gd retention in the brain tissues was not confirmed from the clinical course found by autopsy or on MR images) in the information on patients who received GBCAs reported to the PMDA by Japanese MAHs of GBCAs between the initial marketing and August 31, 2017[20] included 60 cases (74 events) of gadodiamide hydrate, 7 cases (13 events) of meglumine gadopentetate, 1 case (1 event) of gadoxetate sodium, 10 cases (10 events) of gadoteridol, 1 case (2 events) of meglumine gadoterate, and 8 cases (8 events) of gadobutrol. The reported events (MedDRA-PT) included 33 events of “nuclear magnetic resonance imaging abnormal”, 26 events of “biopsy brain abnormal”, 24 events of “nuclear magnetic resonance imaging brain abnormal”, 16 events of “contrast media deposition”, 5 events of “drug clearance decreased”, 3 events of “medication residue present”, and 1 event of “gadolinium deposition disease” (Table 3). There were two foreign cases of Gd retention in the brain tissues confirmed from the clinical courses found by autopsy or MR images in patients who received gadodiamide hydrate, although these are not reported as events related to Gd retention in the brain tissues[20] (The name of the reported adverse reactions was “nephrogenic systemic fibrosis”).

Of these cases, clinical symptoms were reported in 10 cases (36 events) of gadodiamide hydrate, 3 cases (13 events) of meglumine gadopentetate, 3 cases (7 events) of gadoteridol, 1 case (3 events) of meglumine gadoterate, and 3 cases (9 events) of gadobutrol (Table 4); however, there was no clear relationship between all clinical symptoms and Gd retention in the brain tissues.

Table 3 Events related to Gd retention in the brain tissue (number of events)

MedDRA-PT	Linear			Macrocyclic		
	Gadodiamide hydrate	Meglumine gadopentetate	Gadoxetate sodium	Gadoteridol	Meglumine gadoterate	Gadobutrol
Nuclear magnetic	33	0	0	0	0	0

resonance imaging abnormal						
Biopsy brain abnormal	21	0	0	5	0	0
Nuclear magnetic resonance imaging brain abnormal	12	5	0	5	1	1
Contrast media deposition	0	8	1	0	0	7
Drug clearance decreased	5	0	0	0	0	0
Medication residue present	2	0	0	0	1	0
Gadolinium deposition disease	1	0	0	0	0	0

Table 4 Clinical symptoms related to Gd retention in the brain tissues (number of events)

MedDRA-PT	Linear			Macrocyclic		
	Gadodiamide hydrate	Meglumine gadopentetate	Gadoxetate sodium	Gadoteridol	Meglumine gadoterate	Gadobutrol
Nephrogenic systemic fibrosis	5	1	0	0	1	0
Disturbance in attention	2	0	0	2	1	1
Confusional state	2	1	0	2	0	1
Neurological symptom	3	0	0	0	0	0
Altered state of consciousness	1	1	0	1	0	0
Aphasia	1	0	0	1	1	0
Calciphylaxis	2	0	0	0	0	0
Muscular weakness	2	0	0	0	0	0
Tinnitus	1	1	0	0	0	0
Balance disorder	1	1	0	0	0	0
Myalgia	1	1	0	0	0	0
Asthenia	1	0	0	1	0	0
Cognitive disorder	1	0	0	0	0	1
Infection	1	0	0	0	0	0
Dysgeusia	1	0	0	0	0	0
Loss of consciousness	1	0	0	0	0	0
Paraesthesia	1	0	0	0	0	0
Syncope	1	0	0	0	0	0
Ear discomfort	1	0	0	0	0	0
Hypotension	1	0	0	0	0	0
Dysphagia	1	0	0	0	0	0
Dermatitis	1	0	0	0	0	0
Rash	1	0	0	0	0	0
Skin disorder	1	0	0	0	0	0
Skin necrosis	1	0	0	0	0	0
Joint contracture	1	0	0	0	0	0
Meningitis chemical	0	1	0	0	0	0
Gait disturbance	0	1	0	0	0	0
Status epilepticus	0	1	0	0	0	0
Vision blurred	0	1	0	0	0	0

MedDRA-PT	Linear			Macrocyclic		
	Gadodiamide hydrate	Meglumine gadopentetate	Gadoxetate sodium	Gadoteridol	Meglumine gadoterate	Gadobutrol
Amnesia	0	1	0	0	0	0
Pruritus	0	1	0	0	0	0
Feeling abnormal	0	1	0	0	0	0
Condition aggravated	0	0	0	0	0	1
Pain	0	0	0	0	0	1
Dyspnoea	0	0	0	0	0	1
Delirium	0	0	0	0	0	1
Agitation	0	0	0	0	0	1
Hydrophobia	0	0	0	0	0	1

V. PMDA's conclusion based on the investigation results

As a result of investigation of the presently available literature information and case reports related to Gd retention in the brain tissues, the PMDA has confirmed that Gd remains in the brain tissues following GBCAs use. On the other hand, there has been no clear evidence that the clinical symptoms that occurred in patients associated with Gd retention in the brain tissues are related to Gd retention in the brain tissues and no clinical risk has been identified. However, long-term Gd retention in the brain tissues may lead to delayed adverse reactions including nerve disorders, therefore, PMDA has determined that it is appropriate to revise the package inserts of all GBCAs approved in Japan for precaution according to the significance of each such risk from the perspective of minimization of the potential risks associated with Gd retention in the brain tissues. The details of the precaution are as follows.

There have been reports of high signal in the brain sections including dentate nucleus of cerebellum and globus pallidus on unenhanced T1-weighted MR images and detection of Gd in autopsied brain tissues in patients after receiving linear or macrocyclic GBCAs. It is considered that an MRI scan using GBCAs should be limited to the minimum necessary. Therefore, it is determined appropriate to add that the necessity of an MRI scan requiring GBCAs should be carefully determined in the section of "Precautions of Indications" in the package inserts of all GBCAs listed in Attachment 1.

It has also been reported that Gd retention in the brain tissues is mostly confirmed with linear GBCAs, and that no high signal on T1-weighted MR images or less deposits in the brain tissues is found in patients who received macrocyclic GBCAs compared with linear GBCAs. Thus, it is considered appropriate to use macrocyclic GBCAs preferentially when MRI scans with GBCAs are required and to use linear GBCAs when it is determined that the macrocyclic GBCAs cannot be used for the patients for reasons including the incidence of adverse reactions. Therefore, it is determined appropriate to add that linear GBCAs should be used when macrocyclic GBCAs cannot be used in the section of "Precautions of Indications" in the package inserts of liner GBCAs.

Since only gadoxetate sodium has the indication for "contrast imaging of hepatic tumors" among GBCAs and no macrocyclic GBCA can be substituted for it, it was determined that no description is necessary that the drug should be used only when macrocyclic GBCAs cannot be used.

It was determined appropriate to establish the effects of Gd retention in the brain tissues in the Safety Specifications and implement the risk management activities for gadobutrol for which the Risk Management Plan (RMP) has been developed. Moreover, it was also determined appropriate to implement the comparable safety assurance activities for gadodiamide hydrate, meglumine gadopentetate, gadoxetate sodium, gadoteridol, and meglumine gadoterate for which the RMP has not been established.

The Expert Discussion was held regarding the PMDA's opinions described above.

As a result, the expert advisors supported the revision to add that the necessity of MRI scan requiring GBCAs should be carefully determined in the section of "Precautions of Indications" in the package inserts of all GBCAs listed in Attachment 1.

In addition, the expert advisors presented the following opinions regarding the revision to add that linear GBCAs should be used when macrocyclic GBCAs cannot be used in the section of "Precautions of Indications" in the package inserts of liner GBCAs.

Although it is appropriate to consider the incidence of adverse reactions as according to the PMDA's opinions, it is not appropriate to use the wording of "when (macrocyclic GBCAs) cannot be used" because use of linear GBCAs may be considered as appropriate when occurrence of new adverse reactions is concerned after switching to a macrocyclic GBCA in patients previously using a linear GBCA.

Based on the opinions from the expert advisors, the PMDA considered that it is appropriate to alert by the wording of "linear GBCAs should be used when macrocyclic GBCAs are not appropriate" and this was supported by the expert advisors.

Furthermore, the expert advisors supported the PMDA's conclusion that the description that linear GBCAs should be used when use of macrocyclic GBCAs is not appropriate is not necessary in gadoxetate sodium, a linear GBCAs.

The PMDA's decision regarding the RMP of gadobutrol and the safety assurance activities for gadodiamide hydrate, meglumine gadopentetate, gadoxetate sodium, gadoteridol, and meglumine gadoterate was supported by the expert advisors.

VI. Overall assessment

PMDA concluded that it is appropriate to revise the precautions on the package inserts as Attachment 3.

Attachment 1

Gadolinium Contrast Agents

Non-proprietary name	Brand name	MAH	Indications	Dosage and administration
Gadodiamide hydrate	Omniscan Intravenous Injection 32%, Omniscan Intravenous Injection 32% Syringe 5 mL／10 mL／15 mL／20 mL, and the others	Daiichi Sankyo Co. Ltd., and the others	Following contrast imaging in MRI. Contrast imaging of brain and spinal cord Contrast imaging of trunk and extremities	The usual adult dose for intravenous use is 0.2 mL /kg of gadodiamide hydrate. In case of renal examinations, the dose for intravenous use is 0.1 mL /kg of gadodiamide hydrate.
Meglumine gadopentetate	Magnevist IV Injection 10 mL／15 mL／20 mL／30 mL, Magnevist IV Injection Syringe 5 mL／10 mL／15 mL／20 mL, and the others	Bayer Yakuhin, Ltd., and the others	Following contrast imaging in MRI Contrast imaging of brain and spinal cord Contrast imaging of trunk and extremities	The usual adult dose for intravenous use is 0.2 mL /kg of meglumine gadopentetate. In case of renal examinations, the dose for intravenous use is 0.1 mL /kg of meglumine gadopentetate. In case of continuous angiography from the abdomen to the lower extremities, the dose for intravenous use is 0.4 mL /kg of meglumine gadopentetate.
Gadoxetate sodium	EOB・Primovist Injection Syringe 5 mL／10 mL	Bayer Yakuhin, Ltd.	Contrast imaging in MRI of hepatic tumor	The usual adult dose for intravenous use is 0.1 mL /kg of gadoxetate sodium.

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Non-proprietary name	Brand name	MAH	Indications	Dosage and administration
Gadoteridol	ProHance for Intravenous Injection 5 mL／10 mL／15 mL／20 mL, ProHance for Intravenous Injection Syringe 13 mL／17 mL	Bracco-Eisai Co., Ltd.	Following contrast imaging in MRI Contrast imaging of brain and spinal cord Contrast imaging of trunk and extremities	The usual adult dose for intravenous use is 0.2 mL /kg of gadoteridol. In case of renal examinations, the dose for intravenous use is 0.1 mL /kg of gadoteridol. For patients suspected of having a metastatic brain tumor, if no tumor is detected or the contrasting effects are insufficient when a tumor has been detected after the initial dose of 0.2 mL /kg, an additional 0.2 mL /kg may be administered within 30 minutes from the initial dose.
Meglumine gadoterate	Magnescope Intravenous Injection 38% Syringe 10 mL／11 mL／13 mL／15 mL／20 mL	Guerbet Japan K.K.	Following contrast imaging in MRI Contrast imaging of brain and spinal cord Contrast imaging of trunk and extremities	The usual adult dose for intravenous use is 0.2 mL /kg of meglumine gadoterate. In case of renal examinations, the dose for intravenous use is 0.1 mL /kg of meglumine gadoterate. The dose of meglumine gadoterate may be increased up to 0.2 mL /kg where necessary.
Gadobutrol	Gadovist IV Injection 1.0 mol /L Syringe 5 mL／7.5 mL／10 mL	Bayer Yakuhin, Ltd.	Following contrast imaging in MRI Contrast imaging of brain and spinal cord Contrast imaging of trunk and extremities	The usual dose for intravenous use is 0.1 mL /kg of gadobutrol.

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Attachment 2

	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
1	Jost G et al. Invest Radiol. 2016; 51: 83-89.	Signal Increase on Unenhanced T1-Weighted Images in the Rat Brain After Repeated, Extended Doses of Gadolinium-Based Contrast Agents: Comparison of Linear and Macrocyclic Agents.	Non-clinical study Rats	Germany	(i) Gadodiamide hydrate (ii) Meglumine gadopentetate (iii) Dimeglumine gadobenate (iv) Meglumine gadoterate (v) Gadobutrol Controls	(i) 10 rats (ii) 10 rats (iii) 10 rats (iv) 10 rats (v) 10 rats 10 rats	(i)-(v) 10 times (5 days/week for 2 weeks) Intravenous administration 2.5 mmol /kg /time -	Signal intensity increase	(i) Yes (ii) No (moderately increased but there was no significant difference) (iii) Yes (iv) No (v) No -	N/A
2	Robert P et al. Invest Radiol. 2015; 50: 473-480.	T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats: Difference Between Linear and Macrocyclic Agents.	Non-clinical study Rats	France	(i) Gadodiamide hydrate (ii) Meglumine gadoterate Controls	(i) 7 rats (ii) 7 rats 7 rats	(i)(ii) 20 times (4 days/week for 5 weeks) Intravenous administration 0.6 mmol /kg /time -	Signal intensity increase	(i) Yes (ii) No -	Abnormal behavior: No
					(i) Gadodiamide hydrate (ii) Meglumine gadoterate Controls	(i) 7 rats (ii) 7 rats 7 rats		Increased Gd concentration in the brain	(i) Yes (ii) Yes -	

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
3	Robert P et al. Invest Radiol. 2016; 51: 73-82.	Linear Gadolinium-Based Contrast Agents Are Associated With Brain Gadolinium Retention in Healthy Rats.	Non-clinical study Rats	France	(i) Gadodiamide hydrate (ii) Meglumine gadopentetate (iii) Dimeglumine gadobenate (iv) Meglumine gadoterate Controls	(i) 8 rats (ii) 8 rats (iii) 8 rats (iv) 8 rats 8 rats	(i)-(iv) 20 times (4 days/week for 5 weeks) Intravenous administration 0.6 mmol /kg /time -	Signal intensity increase	(i) Yes (ii) Yes (iii) Yes (iv) No -	Abnormal behavior: No
					(i) Gadodiamide hydrate (ii) Meglumine gadopentetate (iii) Dimeglumine gadobenate (iv) Meglumine gadoterate Controls	(i) 8 rats (ii) 8 rats (iii) 8 rats (iv) 8 rats 8 rats		Increased Gd concentration in the brain	(i) Yes (ii) Yes (iii) Yes (iv) No (Gd detected) -	
4	McDonald RJ et al. Radiology. 2017; 285: 536-545.	Comparison of Gadolinium Concentrations within Multiple Rat Organs after Intravenous Administration of Linear versus Macrocyclic Gadolinium Chelates.	Non-clinical study Rats	United States	(i) Gadodiamide hydrate (ii) Dimeglumine gadobenate (iii) Gadoteridol (iv) Gadobutrol Controls	(i) 6 rats (ii) 6 rats (iii) 6 rats (iv) 6 rats 6 rats	(i)-(iv) 20 times (5 days/week for 4 weeks) Intravenous administration 2.5 mmol /kg /time -	Signal intensity increase	(i) Yes (ii) Yes (iii) Yes (iv) Yes -	N/A
					(i) Gadodiamide hydrate (ii) Dimeglumine gadobenate (iii) Gadoteridol (iv) Gadobutrol Controls	(i) 6 rats (ii) 6 rats (iii) 6 rats (iv) 6 rats 6 rats		Increased Gd concentration in the brain	(i) Yes (ii) Yes (iii) Yes (iv) Yes -	

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
5	Rasschaert M et al. Invest Radiol. 2017; 52: 255-264.	Moderate Renal Failure Accentuates T1 Signal Enhancement in the Deep Cerebellar Nuclei of Gadodiamide-Treated Rats.	Non-clinical study Rats	France	Gadodiamide hydrate Controls	20 rats 20 rats	20 times (4 days/week for 5 weeks) Intravenous administration 0.6 mmol /kg /time -	Signal intensity increase	Yes -	Abnormal behavior: No
					Gadodiamide hydrate Controls	20 rats 20 rats		Increased Gd concentration in the brain	Yes -	
6	Lohrke J et al. Invest Radiol. 2017; 52: 324-333.	Histology and Gadolinium Distribution in the Rodent Brain After the Administration of Cumulative High Doses of Linear and Macrocyclic Gadolinium-Based Contrast Agents.	Non-clinical study Rats	Germany	(i) Gadodiamide hydrate (ii) Meglumine gadopentetate (iii) Gadoteridol (iv) Gadobutrol Controls	(i) 10 rats (ii) 10 rats (iii) 10 rats (iv) 10 rats 10 rats	(i)-(iv) 20 times (5 days/week for 4 weeks) Intravenous administration 2.5 mmol /kg /time -	Increased Gd concentration in the brain	(i) Yes (ii) Yes (iii) N/A (Gd detected) (iv) N/A (Gd detected) -	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
7	Smith AP et al. Radiology. 2017; 282: 743-751.	Clearance of Gadolinium from the Brain with No Pathologic Effect after Repeated Administration of Gadodiamide in Healthy Rats: An Analytical and Histologic Study.	Non-clinical study Rats	United Kingdom	(i) Gadodiamide hydrate (ii) Meglumine gadopentetate Controls	(i) 12 rats (high dose) (i) 12 rats (low dose) (ii) 6 rats (high dose) 12 rats	(i) High-dose group: 20 times (4 days/week for 5 weeks) (i) Low-dose group: 10 times (2 days/week for 5 weeks) (ii) High-dose group: 20 times (4 days/week for 5 weeks) Intravenous administration 0.6 mmol /kg /time -	Increased Gd concentration in the brain	(i) Yes (i) Yes (ii) N/A (Gd detected) -	N/A
8	Kartamihardja AA et al. Br J Radiol. 2016; 89: 20160509	Distribution and clearance of retained gadolinium in the brain: differences between linear and macrocyclic gadolinium based contrast agents in a mouse model.	Non-clinical study Mice	Japan	(i) Gadodiamide hydrate (ii) Meglumine gadoterate Controls	(i) 12 mice (ii) 12 mice 6 mice	(i)(ii) 20 times (5 days/week for 4 weeks) Intravenous administration 5 mmol /kg /time -	Increased Gd concentration in the brain	(i) Yes (ii) N/A (Gd detected) -	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
9	Kartamihardja AA et al. Invest Radiol. 2016; 51: 655-660.	Impact of Impaired Renal Function on Gadolinium Retention After Administration of Gadolinium-Based Contrast Agents in a Mouse Model.	Non-clinical study Mice	Japan	(i) Gadodiamide hydrate (ii) Meglumine gadoterate $GdCl_3$ Controls	(i) 13 mice (ii) 13 mice 13 mice 10 mice	(i)(ii) 20 times (5 days/week for 4 weeks) Intravenous administration 5 mmol/kg/time 20 times (5 days/week for 4 weeks) Intravenous administration 0.02 mmol /kg /time -	Increased Gd concentration in the brain	(i) Yes (ii) N/A (Gd detected) - -	N/A
10	Frenzel T et al. Invest Radiol. 2017; 52: 396-404.	Quantification and Assessment of the Chemical Form of Residual Gadolinium in the Brain After Repeated Administration of Gadolinium-Based Contrast Agents: Comparative Study in Rats.	Non-clinical study Rats	Germany	(i) Gadodiamide hydrate (ii) Meglumine gadopentetate (iii) Dimeglumine gadobenate (iv) Meglumine gadoterate (v) Gadobutrol Controls	(i) 10 rats (ii) 10 rats (iii) 10 rats (iv) 10 rats (v) 10 rats 10 rats	(i)-(v) 10 times (5 days/week for 2 weeks) Intravenous administration 2.5 mmol /kg /time -	Increased Gd concentration in the brain	(i)-(v) N/A -	N/A
11	Bussi S et al. J Magn Reson Imaging. 2017.	Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats.	Non-clinical study Rats	Italy	(i) Gadoteridol (ii) Meglumine gadoterate (iii) Gadobutrol Controls	(i) 15 rats (ii) 15 rats (iii) 15 rats 5 rats	(i)-(iii) 20 times (4 days/week for 5 weeks) Intravenous administration 0.6 mmol /kg /time -	Increased Gd concentration in the brain	(i) N/A (Gd detected) (ii) Yes (iii) Yes -	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
12	Kanda T et al. Radiology. 2014; 270: 834-841.	High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material.	Clinical study	Japan	Gadodiamide hydrate, meglumine gadopentetate Controls	19 patients 16 patients	6-12 times (mean 7.1 times) Intravenous administration 7.5 mmol /kg /time -	Signal intensity increase	Yes -	N/A
13	Ichikawa S et al. Invest Radiol. 2017; 52: 389-395.	Contrast Agent-Induced High Signal Intensity in Dentate Nucleus on Unenhanced T1-Weighted Images: Comparison of Gadodiamide and Gadoxetic Acid.	Clinical study	Japan	(i) Gadodiamide hydrate (ii) Gadoxetate sodium Controls	(i) 33 patients (≥ 5 times) (ii) 33 patients (1 time) (ii) 33 patients (≥ 5 times) 33 patients	(i) 5-15 times Intravenous administration 0.1 mmol /kg /time (ii) 1 time Intravenous administration 0.025 mmol /kg /time (ii) 5-15 times Intravenous administration 0.025 mmol /kg /time -	Signal intensity increase	(i) Yes (ii) No (ii) No -	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
14	Ramalho J et al. Radiology. 2015; 276: 836-844.	High Signal Intensity in Globus Pallidus and Dentate Nucleus on Unenhanced T1-weighted MR Images: Evaluation of Two Linear Gadolinium-based Contrast Agents.	Clinical study	United States	(i) Gadodiamide hydrate (ii) Dimeglumine gadobenate	(i) 23 patients (ii) 46 patients	(i) 3 -11 times (mean 5.0 ± 2.4 times) (ii) 3 -11 times (mean 4.6 ± 2.1 times) Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	(i) Yes (ii) Yes	N/A
15	Errante Y et al. Invest Radiol. 2014; 49: 685-690.	Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation.	Clinical study	Italy	Gadodiamide hydrate	75 patients	2-21 times Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	Yes	N/A

N/A: Not evaluated (including unknown cases)

	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
16	Quattrocchi CC et al. Invest Radiol. 2015; 50: 470-472.	Gadodiamide and Dentate Nucleus T1 Hyperintensity in Patients With Meningioma Evaluated by Multiple Follow-Up Contrast-Enhanced Magnetic Resonance Examinations With No Systemic Interval Therapy.	Clinical study	Italy	Gadodiamide hydrate	A: 10 patients B: 28 patients C: 8 patients Total: 46 patients	A: 1 time B: 1-5 times C: ≥ 6 times Intravenous administration Single dose: N/A	Signal intensity increase	A:- B: No C: Yes	Complaints of neurological symptoms: No
17	Weberling LD et al. Invest Radiol. 2015; 50: 743-748.	Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-Weighted Images After Dimeglumine gadobenate Administration.	Clinical study	Germany	Dimeglumine gadobenate	50 patients	5 -15 times (mean 7.7 ± 3.2 times) Intravenous administration 15 mL /time or 20 mL /time (0.5 M)	Signal intensity increase	Yes	N/A
18	Kuno H et al. Radiology. 2017; 283: 195-204.	Global and Regional Brain Assessment with Quantitative MR Imaging in Patients with Prior Exposure to Linear Gadolinium-based Contrast Agents.	Clinical study	United States	Meglumine gadopentetate Controls	9 patients 26 patients	1-8 times Route of administration: N/A Single dose: N/A -	Reduction of T1 and T2 relaxation times	Yes -	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
19	Hu HH et al. Pediatr Radiol. 2016; 46: 1590-1598.	Increased signal intensities in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evidence in children undergoing multiple gadolinium MRI exams.	Clinical study	United States	Meglumine gadopentetate Controls	21 patients 21 patients	5-37 times Intravenous administration 0.1 mmol /kg /time -	Signal intensity increase	Yes -	N/A
20	Flood TF et al. Radiology. 2017; 282: 222-228.	Pediatric Brain: Repeated Exposure to Linear Gadolinium-based Contrast Material Is Associated with Increased Signal Intensity at Unenhanced T1-weighted MR Imaging.	Clinical study	United States	Meglumine gadopentetate Controls	Comparison with controls: 30 patients Comparison between initial dose and final dose: 16 patients 57 patients	Comparison with controls: Mean 5.9 ± 2.7 times Comparison between initial dose and final dose: Mean 5.8 ± 2.1 times Intravenous administration Single dose: N/A -	Signal intensity increase	Yes Yes -	N/A
21	Zhang Y et al. Radiology. 2017; 282: 516-525.	Extent of Signal Hyperintensity on Unenhanced T1-weighted Brain MR Images after More than 35 Administrations of Linear Gadolinium-based Contrast Agents.	Clinical study	United States	Gadodiamide hydrate, meglumine gadopentetate, dimeglumine gadobenate	13 patients	39-59 times (mean 43 ± 5 times) Route of administration: N/A Single dose: N/A	Signal intensity increase	Yes	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
22	Kahn J et al. Radiology. 2017; 282: 708-716.	Is There Long-term Signal Intensity Increase in the Central Nervous System on T1-weighted Images after MR Imaging with the Hepatospecific Contrast Agent Gadoxetic Acid? A Cross-sectional Study in 91 Patients.	Clinical study	Germany	Gadoxetate sodium Controls	A1: 32 patients A2: 27 patients A3: 32 patients 52 patients	A1: 1-4 times (mean 2.8 ± 1.14 times) A2: 5-10 times (mean 6.7 ± 1.38 times) A3: 11-37 times (mean 16.8 ± 6.5 times) Intravenous administration Single dose: N/A -	Signal intensity increase	No No Yes -	N/A
23	Conte G et al. Eur Radiol. 2017; 27: 4372-4378.	Signal intensity change on unenhanced T1-weighted images in dentate nucleus and globus pallidus after multiple administrations of gadoxetate disodium: an intraindividual comparative study.	Clinical study	Italy	Gadoxetate sodium	18 patients	2-18 times (mean 11.11 ± 5.59 times) Intravenous administration 0.025 mmol /kg /time	Signal intensity increase	No	N/A
24	Roberts DR et al. AJNR Am J Neuroradiol. 2016; 37: 2340-2347.	Pediatric Patients Demonstrate Progressive T1-Weighted Hyperintensity in the Dentate Nucleus following Multiple Doses of Gadolinium-Based Contrast Agent.	Clinical study	United States	Meglumine gadopentetate	16 patients	4-16 times Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	Yes	N/A

N/A: Not evaluated (including unknown cases)

	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
25	Cao Y et al. Invest Radiol. 2016; 51: 677-682.	Effect of Renal Function on Gadolinium-Related Signal Increases on Unenhanced T1-Weighted Brain Magnetic Resonance Imaging.	Clinical study	United States	Gadodiamide hydrate, meglumine gadopentetate, dimeglumine gadobenate	50 patients (Dialysis patients, patients with eGFR >60 mL /m^2: 25 patients, respectively)	Mean 1.8 ± 1 times Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	Yes	N/A
26	Ramalho J et al. AJNR Am J Neuroradiol. 2016; 37: 1427-1431.	T1 Signal-Intensity Increase in the Dentate Nucleus after Multiple Exposures to Gadodiamide: Intraindividual Comparison between 2 Commonly Used Sequences.	Clinical study	United States	Gadodiamide hydrate	18 patients	2-10 times (mean 4.78 ± 2.51 times) Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	Yes	N/A
27	Tanaka M et al. Eur Neurol. 2016; 75: 195-198.	Increased Signal Intensity in the Dentate Nucleus of Patients with Multiple Sclerosis in Comparison with Neuromyelitis Optica Spectrum Disorder after Multiple Doses of Gadolinium Contrast.	Clinical study	Japan	Gadodiamide hydrate, meglumine gadopentetate	27 patients	≥ 10 times Route of administration: N/A Single dose: N/A	Signal intensity increase	Yes	Cerebellar manifestations: No

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
28	Forslin Y et al. AJNR Am J Neuroradiol. 2017; 38: 1311-1316.	Retention of Gadolinium-Based Contrast Agents in Multiple Sclerosis: Retrospective Analysis of an 18-Year Longitudinal Study.	Clinical study	Sweden	Gadodiamide hydrate, meglumine gadopentetate (6 patients with pretreatment with meglumine gadoterate) Controls	23 patients 23 patients	3-12 times Intravenous administration Single dose: N/A -	Signal intensity increase	Yes -	Decrease of verbal fluency: Yes (relationship with drugs is unknown)
29	Schneider GK et al. AJNR Am J Neuroradiol. 2017; 38: 1799-1806.	T1 Signal Measurements in Pediatric Brain: Findings after Multiple Exposures to Dimeglumine gadobenate for Imaging of Nonneurologic Disease.	Clinical study	Germany	Dimeglumine gadobenate Controls	34 patients 24 patients	5-15 times (mean 7.8 ± 2.9 times) Intravenous administration 0.05 mmol /kg /time -	Signal intensity increase	No -	N/A
30	Roberts DR et al. Brain Dev. 2016; 38: 331-336.	Progressive increase of T1 signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in the pediatric brain exposed to multiple doses of gadolinium contrast.	Clinical study	United States	Meglumine gadopentetate	1 patient	6 times Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	Yes	N/A

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31	Radbruch A et al. Radiology. 2017; 282: 699-707.	No Signal Intensity Increase in the Dentate Nucleus on Unenhanced T1-weighted MR Images after More than 20 Serial Injections of Macrocyclic Gadolinium-based Contrast Agents.	Clinical study	Germany	Meglumine gadoterate, gadobutrol	33 patients	Mean 23.03 ± 4.20 times Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	No	N/A
32	Tibussek D et al. Radiology. 2017; 285: 223-230.	Gadolinium Brain Deposition after Macrocyclic Gadolinium Administration: A Pediatric Case-Control Study.	Clinical study	Germany	Meglumine gadoterate, gadoteridol Controls	24 patients 24 patients	9-24 times (mean 14.21 times) Intravenous administration 0.1 mmol /kg /time -	Signal intensity increase	No -	N/A
33	Radbruch A et al. Invest Radiol. 2015; 50: 805-810.	High-Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-Weighted Images: Evaluation of the Macrocyclic Gadolinium-Based Contrast Agent Gadobutrol.	Clinical study	Germany	Gadobutrol	30 patients	5-19 times (mean 7.3 ± 3.1 times) Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	No	N/A

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34	Eisele P et al. Medicine (Baltimore). 2016; 95: e4624.	Lack of increased signal intensity in the dentate nucleus after repeated administration of a macrocyclic contrast agent in multiple sclerosis: An observational study.	Clinical study	Germany	Meglumine gadoterate	41 patients	6-12 times (mean 6.8 times) Intravenous administration Single dose: N/A	Signal intensity increase	No	N/A
35	Langner S et al. Eur Radiol. 2017; 27: 3687-3693.	Repeated intravenous administration of gadobutrol does not lead to increased signal intensity on unenhanced T1-weighted images-a voxel-based whole brain analysis.	Clinical study	Germany	Gadobutrol	217 patients	1-5 times Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	No	N/A
36	Yoo RE et al. Invest Radiol. 2017.	Evaluation of Gadolinium Retention After Serial Administrations of a Macrocyclic Gadolinium-Based Contrast Agent (Gadobutrol): A Single-Institution Experience With 189 Patients.	Clinical study	South Korea	Gadobutrol	189 patients (< 6 times: 126 patients, ≥ 6 times: 63 patients)	2-50 times (mean 5.9 ± 6.3 times) Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	No	N/A

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37	Müller A et al. Clin Neuroradiol. 2017.	Brain relaxometry after macrocyclic Gd-based contrast agent.	Clinical study	Germany	Gadobutrol	17 patients	5-14 times (mean 8 times) Intravenous administration 0.1 mmol /kg /time	Signal intensity increase Reduction of T1 relaxation time	No No	N/A
38	Cao Y et al. AJR Am J Roentgenol. 2016; 206: 414-419.	Signal Change in the Dentate Nucleus on T1-Weighted MR Images After Multiple Administrations of Gadopentetate Dimeglumine Versus Gadobutrol.	Clinical study	United States	(i) Meglumine gadopentetate (ii) Gadobutrol	(i) 25 patients (ii) 25 patients	(i) 6-23 times (mean 12.1 ± 5.2 times) (ii) 6-16 times (mean 7.8 ± 2.4 times) Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	(i) Yes (ii) No	N/A
39	Kasahara S et al. Radiology. 2011; 258: 222-228.	Hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with a history of brain irradiation.	Clinical study	Japan	N/A	N/A	N/A	N/A	N/A	N/A
40	Tedeschi E et al. Eur Radiol. 2016; 26: 4577-4584.	In vivo dentate nucleus MRI relaxometry correlates with previous administration of Gadolinium-based contrast agents.	Clinical study	Italy	Gd-based contrast agents containing meglumine gadopentetate, meglumine gadoterate and gadobutrol	74 patients	1-15 times (mean 6.0 ± 3.8 times) Route of administration: N/A Single dose: N/A	Reduction of T1 relaxation time	Yes	N/A

N/A: Not evaluated (including unknown cases)

	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
41	Radbruch A et al. Radiology. 2017; 283: 828-836.	Pediatric Brain: No Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-weighted MR Images after Consecutive Exposure to a Macrocyclic Gadolinium-based Contrast Agent.	Clinical study	Germany	Meglumine gadoterate	41 patients	Mean 8.6 ± 3.9 times Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	No	N/A
42	Stojanov DA et al. Eur Radiol. 2016; 26: 807-815.	Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol.	Clinical study	Serbia	Gadobutrol	58 patients	4-6 times (mean 4.74 ± 0.72 times) Intravenous administration 0.1 mmol /kg /time	Signal intensity increase	Yes (no significant visual difference)	N/A

N/A: Not evaluated (including unknown cases)

	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
43	Rossi Espagnet MC et al. Pediatr Radiol. 2017; 47: 1345-1352.	Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children.	Clinical study	Italy	Meglumine gadoterate Controls	50 patients 59 patients	6-18 times (mean 10 ± 2.8 times) Intravenous administration 0.1 mmol /kg /time -	Signal intensity increase	Yes (no significant visual difference) -	N/A
44	Stojanov DA. Eur Radiol. 2016; 26: 818-819.	Reply to Letter to the Editor re: Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: Correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol.	Letter to the editor	Serbia	N/A	N/A	N/A	N/A	N/A	N/A

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45	Runge VM. Invest Radiol. 2015; 50: 811.	Macrocyclic Versus Linear Gadolinium Chelates.	Commentary	Switzerland	N/A	N/A	N/A	N/A	N/A	N/A
46	Agris J et al. Eur Radiol. 2016; 26: 816-817.	What Evidence Is There That Gadobutrol Causes Increasing Signal Intensity within the Dentate Nucleus and Globus Pallidus on Unenhanced T1W MRI in Patients with RRMS?	Letter to the editor	United States	N/A	N/A	N/A	N/A	N/A	N/A
47	Kanda T et al. Radiology. 2015; 275: 803-809.	High Signal Intensity in Dentate Nucleus on Unenhanced T1-weighted MR Images: Association with Linear versus Macrocyclic Gadolinium Chelate Administration.	Clinical study	Japan	(i) Meglumine gadopentetate (i) Meglumine gadopentetate and (ii) Gadoteridol (ii) Gadoteridol Controls	(i) 23 patients (i) and (ii) 14 patients (ii) 36 patients 54 patients	(i) Median: 2 times, Maximum: 11 times (i) Median: 2 times, Maximum: 5 times and (ii) Median: 3 times, Maximum 8 times (i) Median: 2 times, Maximum: 15 times Intravenous administration 0.1 mmol /kg /time -	Signal intensity increase	(i) Yes (i) and (ii) N/A (2 patients with increased signal intensity by visual assessment) (ii) No -	N/A

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48	Radbruch A et al. Radiology. 2015; 275: 783-791.	Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent.	Clinical study	Germany	(i) Meglumine gadopentetate (ii) Meglumine gadoterate	(i) 50 patients (ii) 50 patients	(i) Mean 7.32 ± 1.83 times (ii) Mean 7.06 ± 1.20 times Intravenous administration (i) 15-20 mL /time (ii) 0.1 mmol /kg /time	Signal intensity increase	(i) Yes (ii) No	N/A
49	Schlemm L et al. Mult Scler. 2017; 23: 963-972.	Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients.	Clinical study	Germany	(i) Meglumine gadopentetate (ii) Gadobutrol	(i) 49 patients (ii) 48 patients	(i) 1-3 times (mean 2.08 times) (ii) 1-3 times (mean 2.02 times) Intravenous administration (i): 20 mL/time (ii): 0.1 mL /kg /time	Signal intensity increase	(i) Yes (ii) No	N/A
50	Bae S et al. Eur Radiol. 2017; 27: 3353-3361.	Gadolinium deposition in the brain: association with various GBCAs using a generalized additive model.	Clinical study	South Korea	(i) Gadodiamide hydrate (ii) Meglumine gadopentetate (iii) Meglumine gadoterate (iv) Gadobutrol	122 patients (Linear only: 6 patients, macrocyclic only: 44 patients, both: 72 patients)	12-65 times (mean 29.0 times) Intravenous administration 0.2 mmol /kg /time	Signal intensity increase	(i) Yes (ii) Yes (iii) No (iv) No	N/A
51	Radbruch A et al. Invest Radiol. 2016; 51: 683-690.	Intraindividual Analysis of Signal Intensity Changes in the Dentate Nucleus After Consecutive Serial Applications of Linear and Macrocyclic Gadolinium-Based Contrast Agents.	Clinical study	Germany	(i) Meglumine gadopentetate (ii) Meglumine gadoterate (iii) Gadobutrol	(i) 36 patients (ii) 12 mice (iii) 36 patients	(i) Mean 6.0 ± 1.9 times (ii) Mean 6.8 ± 1.4 times (iii) Mean 6.0 ± 1.9 times Intravenous administration (i) 15 mL /time or 20 mg /time (ii) 0.1 mmol /kg /time (iii) 0.1 mmol /kg /time	Signal intensity increase	(i) Yes (ii) No (iii) No	N/A

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52	Adin ME et al. AJNR Am J Neuroradiol. 2015; 36: 1859-1865.	Hyperintense Dentate Nuclei on T1-Weighted MRI: Relation to Repeat Gadolinium Administration.	Clinical study	United States	Gadodiamide hydrate, meglumine gadopentetate, dimeglumine gadobenate, gadoversetamide, gadoteridol, gadobutrol	184 patients	1-60 times (mean 14.55 times) Intravenous administration Single dose: N/A	Signal intensity increase	Yes	N/A
53	Kanda T et al. Radiology. 2015; 276: 228-232.	Gadolinium-based Contrast Agent Accumulates in the Brain Even in Subjects without Severe Renal Dysfunction: Evaluation of Autopsy Brain Specimens with Inductively Coupled Plasma Mass Spectroscopy.	Clinical study	Japan	Gadodiamide hydrate, meglumine gadopentetate, gadoteridol Controls	5 patients 5 patients	2-4 times Intravenous administration 0.1 mmol /kg /time -	Increased Gd concentration in the brain	Yes -	N/A
54	Murata N et al. Invest Radiol. 2016; 51: 447-453.	Macrocyclic and Other Non-Group 1 Gadolinium Contrast Agents Deposit Low Levels of Gadolinium in Brain and Bone Tissue: Preliminary Results From 9 Patients With Normal Renal Function.	Clinical study	United States	(i) Gadoxetate sodium (ii) Dimeglumine gadobenate (iii) Gadoteridol (iv) Gadobutrol Controls	(i) 1 patient (ii) 1 patient (iii) 5 patients (iv) 2 patients 9 patients	(i) 10 times (ii) 1 time (iii) 1-11 times (iv) 1-2 times Intravenous administration (i) Single dose: N/A (ii) 0.1 mmol /kg /time (iii) 0.1 mmol /kg /time (iv) 0.1 mmol /kg /time -	Increased Gd concentration in the brain	(i) Yes (ii) Yes (iii) Yes (iv) Yes -	N/A

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55	McDonald JS et al. JAMA Pediatr. 2017; 171: 705-707.	Intracranial Gadolinium Deposition Following Gadodiamide-Enhanced Magnetic Resonance Imaging in Pediatric Patients: A Case-Control Study.	Clinical study	United States	Gadodiamide hydrate Controls	3 patients 3 patients	4, 8, 9 times Intravenous administration 0.1 mmol /kg /time -	Increased Gd concentration in the brain	N/A (Gd detected) -	N/A
56	McDonald RJ et al. Radiology. 2015; 275: 772-782.	Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging.	Clinical study	United States	Gadodiamide hydrate Controls	13 patients 10 patients	4-29 times Intravenous administration 0.1 mmol /kg /time -	Signal intensity increase	Yes -	N/A
					Gadodiamide hydrate Controls	13 patients 10 patients		Increased Gd concentration in the brain	Yes -	
57	McDonald JS et al. Radiology. 2017. 285; 546-554.	Gadolinium Deposition in Human Brain Tissues after Contrast-enhanced MR Imaging in Adult Patients without Intracranial Abnormalities.	Clinical study	United States	Gadodiamide hydrate Controls	5 patients 10 patients	4-18 times Intravenous administration 0.1 mmol /kg /time -	Increased Gd concentration in the brain	Yes -	N/A
58	Murata N et al. Magn Reson Imaging. 2016; 34: 1359-1365.	Gadolinium tissue deposition in brain and bone.	Review	United States	N/A	N/A	N/A	N/A	N/A	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
59	Welk B et al. JAMA. 2016; 316: 96-98.	Association Between Gadolinium Contrast Exposure and the Risk of Parkinsonism.	Clinical study	Canada	N/A	Gd-based contrast agent-treated: 99,739 patients Untreated: 146,818 patients	N/A	N/A	N/A	Parkinsonism: No
60	Olchowy C et al. PLoS One. 2017; 12: e0171704.	The presence of the gadolinium-based contrast agent depositions in the brain and symptoms of gadolinium neurotoxicity - A systematic review.	Review	Poland	N/A	N/A	N/A	N/A	N/A	N/A
61	Roberts DR et al. Neurology. 2017; 88: 1206-1208.	Distribution map of gadolinium deposition within the cerebellum following GBCA administration.	Clinical study	United States	Gadodiamide hydrate, meglumine gadopentetate	1 patient	4 times Route of administration: N/A Single dose: N/A	Increased Gd concentration in the brain	N/A (Gd detected)	N/A

N/A: Not evaluated (including unknown cases)

	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
62	Barbieri S et al. Contrast Media Mol Imaging. 2016; 11: 245-250.	High signal intensity in dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in three patients with impaired renal function and vascular calcification.	Clinical study	Switzerland	Patient 1: (i) Gadodiamide hydrate (ii) Meglumine gadopentetate (iii) Gadoteridol (iv) Gadobutrol Patient 2: (i) Gadodiamide hydrate (iii) Gadoteridol (v) Meglumine gadoterate Patient 3: (i) Gadodiamide hydrate (iii) Gadoteridol (iv) Gadobutrol	3 patients	Patient 1: 8 times Patient 2: 4 times Patient 3: 7 times Intravenous administration Patient 1: (i) 18 mmol + 16 mmol (ii) 10 mmol + 10 mmol (iii) 16 mmol + 16 mmol+15 mmol (iv) 7.5 mmol Patient 2: (i) 15 mmol + 15 mmol (iii) 16 mmol (v) 7.5 mmol Patient 3: (i) 15 mmol (iii) 16 mmol + 16 mmol+5 mmol + 5 mmol (iv) 5 mmol	Signal intensity increase	N/A (Signal intensity increased)	Signs of transient nerve disorders: Yes (relationship with drugs is unknown)
63	Khant ZA et al. Magn Reson Med Sci. 2017; 16: 84-86.	T1 Shortening in the Cerebral Cortex after Multiple Administrations of Gadolinium-based Contrast Agents.	Clinical study	Japan	(i) Meglumine gadopentetate (ii) Meglumine gadoterate (iii) Gadoteridol	1 patient	Number of doses between 2003 and 2014 (i) 59 times (ii) 24 times (iii) 3 times Intravenous administration Single dose: N/A	Signal intensity increase	N/A (Signal intensity increased)	N/A

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	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
64	Kanda T et al. Jpn J Radiol. 2016; 34: 258-266.	Contribution of metals to brain MR signal intensity: review articles.	Review	Japan	N/A	N/A	N/A	N/A	N/A	N/A
65	Kanda T et al. Jpn J Radiol. 2016; 34: 3-9.	Brain gadolinium deposition after administration of gadolinium-based contrast agents.	Review	Japan	N/A	N/A	N/A	N/A	N/A	N/A
66	Stojanov D et al. Neuroradiology. 2016; 58: 433-441.	Gadolinium deposition within the dentate nucleus and globus pallidus after repeated administrations of gadolinium-based contrast agents-current status.	Review	Serbia	N/A	N/A	N/A	N/A	N/A	N/A
67	Frenzel T et al. Invest Radiol. 2008; 43: 817-828.	Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37°C.	Non-clinical study	Germany	Gadodiamide hydrate Meglumine gadopentetate Gadoxetate sodium Dimeglumine gadobenate Gadoversetamide Gadoteridol Meglumine gadoterate Gadobutrol	N/A	N/A	N/A	N/A	N/A

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68	Ramalho J et al. Magn Reson Imaging. 2016; 34: 1355–1358.	Technical aspects of MRI signal change quantification after gadolinium-based contrast agents' administration.	Review	United States	N/A	N/A	N/A	N/A	N/A	N/A
69	Runge VM. Invest Radiol. 2016; 51: 273-279.	Safety of the Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging, Focusing in Part on Their Accumulation in the Brain and Especially the Dentate Nucleus.	Review	Switzerland	N/A	N/A	N/A	N/A	N/A	N/A
70	Jost G et al. Eur Radiol. 2017; 27: 2877-2885.	Penetration and distribution of gadolinium-based contrast agents into the cerebrospinal fluid in healthy rats: a potential pathway of entry into the brain tissue.	Non-clinical study Rats	Germany	Gadodiamide hydrate Meglumine gadopentetate Dimeglumine gadobenate Gadoteridol Meglumine gadoterate Gadobutrol Gadomer Controls	12 rats 12 rats 12 rats 12 rats 12 rats 12 rats 12 rats 12 rats	Single dose Intravenous administration 1.8 mmol /kg /time	N/A	N/A	N/A

N/A: Not evaluated (including unknown cases)

	Data		Non-clinical/ clinical studies	Country	Products investigated (non-proprietary name)	Number of subjects	Usage (Number of doses/route of administration/dose)	Criteria for evaluation	Results (Yes: With significant difference, No: Without significant difference)	Presence of clinical symptoms
71	Lancelot E. Invest Radiol. 2016; 51: 691-700.	Revisiting the Pharmacokinetic Profiles of Gadolinium-Based Contrast Agents: Differences in Long-Term Biodistribution and Excretion.	Non-clinical and clinical studies	France	Gadodiamide hydrate Meglumine gadopentetate Gadoxetate sodium Dimeglumine gadobenate Gadoteridol Meglumine gadoterate Gadobutrol	N/A	N/A	N/A	N/A	N/A
72	Pietsch H et al. Invest Radiol. 2009; 44: 226-233.	Impact of renal impairment on long-term retention of gadolinium in the rodent skin following the administration of gadolinium-based contrast agents.	Non-clinical study Rats	Germany	Gadodiamide hydrate Meglumine gadopentetate Gadoversetamide Gadobutrol	12 rats 12 rats 6 rats 6 rats	5 consecutive doses Intravenous administration 2.5 mmol /kg /time	N/A	N/A	N/A
73	Fretellier N et al. Invest Radiol. 2011; 46: 292-300.	Comparative in vivo dissociation of gadolinium chelates in renally impaired rats: a relaxometry study.	Non-clinical study Rats	France	Gadodiamide hydrate Gadodiamide hydrate (unformulated) Meglumine gadoterate	8 rats 10 rats 8 rats	5 consecutive doses Intravenous administration 2.5 mmol /kg /time	N/A	N/A	N/A
74	Naganawa S et al. Magn Reson Med Sci. 2017; 16: 61-65.	Gd-based Contrast Enhancement of the Perivascular Spaces in the Basal Ganglia.	Clinical study	Japan	Gadodiamide hydrate Gadoteridol	12 patients 15 patients	Single dose Intravenous administration 0.1 mmol /kg /time or 0.2 mL /kg /time	N/A	N/A	N/A

N/A: Not evaluated (including unknown cases)

Attachment 3

[Proposed revision] Gadodiamide hydrate

Underlined added

Current version	Proposed revision
No related description	<Precautions of Indications> 1. It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium-based contrast agents should be determined carefully. 2. It has been reported that more gadolinium remained in the brain with linear gadolinium-based contrast agents containing this drug than with macrocyclic gadolinium-based contrast agents. This drug should be administered when macrocyclic gadolinium-based contrast agents are not appropriate.

[Proposed revision] Meglumine gadopentetate

Underlined added

Current version	Proposed revision
No related description	<Precautions of Indications> 1. It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium-based contrast agents should be determined carefully. 2. It has been reported that more gadolinium remained in the brain with linear gadolinium-based contrast agents containing this drug than with macrocyclic gadolinium-based contrast agents. This drug should be administered when macrocyclic gadolinium-based contrast agents are not appropriate.

[Proposed revision] Gadoxetate sodium

Underlined added

Current version	Proposed revision
No related description	<Precautions of Indications> It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium-based contrast agents should be determined carefully.

[Proposed revision] Gadoteridol

Underlined added

Current version	Proposed revision
No related description	<Precautions of Indications> It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium-based contrast agents should be determined carefully.

[Proposed revision] Meglumine gadoterate

Underlined added

Current version	Proposed revision
No related description	<Precautions of Indications> It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium-based contrast agents should be determined carefully.

[Proposed revision] Gadobutrol

Underlined added

Current version	Proposed revision
No related description	<Precautions of Indications> It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium-based contrast agents should be determined carefully.