Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

Date:	June 11, 2019
Safety Evaluator:	Sarah Kang, Pharm.D, MSP, BCPS Division of Pharmacovigilance II (DPV II)
Medical Officer:	Ivone Kim, MD, FAAP DPV I
Team Leader:	Neha Gada, Pharm.D, BCPS DPV II
Deputy Division Director:	Ida-Lina Diak, Pharm.D., MS DPV II
Product Name:	Dotarem (gadoterate meglumine)
Pediatric Labeling Approval Date:	August 25, 2017
Application Type/Number:	NDA 204781
Applicant/Sponsor:	Guerbet
OSE RCM #:	2019-458

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for gadoterate meglumine (Dotarem) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events (AEs) associated with gadoterate meglumine in pediatric patients.

The FDA approved gadoterate meglumine on March 20, 2013 for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients 2 years of age and older to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. On August 25, 2017, Dotarem's sponsor, Guerbet, fulfilled the post marketing requirement (PMR) to examine gadoterate meglumine pharmacokinetics (PK) in patients 0 to 23 months old, and gained approval to extend the indication to include term neonates. FDA revised the Pediatric Use section of the Dotarem label to reflect the PMR study findings; the pediatric labeling change triggered this safety review.

We reviewed all serious FAERS reports with gadoterate meglumine in pediatric patients through age 16 years from April 1, 2015 through February 28, 2019. We chose this start date to capture all reports from the data lock date of a previous OSE review.[1]

Our FAERS search retrieved 43 reports. We did not identify any deaths associated with gadoterate meglumine. After reviewing the reports, we excluded all 43 because they described AEs that are well labeled (n=37; e.g., hypersensitivity, nausea, and dizziness with malaise), described AEs with compelling alternative etiologies (n=2), had limited information (n=2), did not describe an AE (n=1), or were duplicate reports (n=1).

We did not identify any new safety signals or apparent increased severity of any labeled AEs associated with gadoterate meglumine.

DPV recommends no regulatory action at this time and will continue to monitor all AEs associated with the use of gadoterate meglumine.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for gadoterate meglumine (Dotarem) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events (AEs) associated with gadoterate meglumine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Gadoterate meglumine is gadolinium-based contrast agent. FDA first approved gadoterate meglumine on March 20, 2013 for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. Gadoterate meglumine is 0.5 mmol/mL contains 376.9 mg/mL of gadoterate meglumine and is available in vials and pre-filled syringes.

OSE previously evaluated postmarketing AE reports with a serious outcome and drug utilization data for gadoterate meglumine in pediatric patients. OSE's evaluation,[1] dated August 12, 2015, was prompted by the pediatric labeling changes on March 20, 2013, which stated "The safety and efficacy of Dotarem at a single dose of 0.1 mmol/kg have been established in pediatric patients from 2 to 17 years of age. No dosage adjustment according to age is necessary in this population." OSE's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for AEs with gadoterate meglumine. FDA presented OSE's evaluation to the Pediatric Advisory Committee (PAC) on September 16, 2015.

On August 25, 2017, Dotarem's sponsor, Guerbet, fulfilled the post marketing requirement (PMR) to examine the pharmacokinetics (PK) in patients 0 to 23 months old, and gained approval to extend the indication to include term neonates.[2] FDA revised the Pediatric Use section of the Dotarem label, incorporating the results of 1) the pivotal PMR study, an open-label, non-randomized, comparative (before and after injection of contrast agent), multicenter study (DGD-44-063) in pediatric patients aged < 2 years (term newborn infants defined as ≥37 weeks amenorrhea to toddlers 23 months of age) undergoing a contrast enhanced MRI with a Dotarem intravenous injection of 0.1 mmol/kg,[3] and 2) three supportive non-randomized studies (DGD-03-015, DGD-03-016, DGD-03-029) which included pediatric patients of <2 years of age.[2] The pediatric labeling change triggered this safety review. Safety and efficacy data reflected in the pediatric labeling change for Dotarem are described below:[4]

- The safety and efficacy of Dotarem at a single dose of 0.1 mmol/kg have been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data in 133 pediatric patients 2 years of age and older, and clinical data in 52 pediatric patients birth to less than 2 years of age that supported extrapolation from adult data [see *Clinical Studies (14)*]. Adverse reactions in pediatric patients were similar to those reported in adults [see *Adverse Reactions (6.1)*]. No dosage adjustment according to age is necessary in pediatric patients [See *Dosage and Administration (2.1),*

Pharmacokinetics (12.3)]. The safety of Dotarem has not been established in preterm neonates.

- A non-randomized study with 28 pediatric patients under 2 years of age who were referred for contrast MRI of the CNS supported extrapolation of CNS efficacy findings from adults and older children. CNS lesions were identified in 16 of these 28 patients on paired pre- and post-contrast images compared to 15 patients on pre-contrast images alone. In the 16 patients who had identifiable lesions, the scores for the co-endpoints of lesion visualization were improved for at least one lesion on paired pre- and post-contrast images compared to pre-contrast images in 8 out of 16 (50%) patients for lesion border delineation, 8 out of 16 (50%) patients for lesion internal morphology, and 14 out of 16 (88%) patients for lesion contrast enhancement.

1.2 RELEVANT LABELED SAFETY INFORMATION[4]

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full prescribing information for complete boxed warning

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73m2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).**

---------- CONTRAINDICATIONS ----------

Clinically important hypersensitivity reactions to DOTAREM. (4)

---------- WARNINGS AND PRECAUTIONS ----------

• Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk. (5.1)

• Hypersensitivity: Anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred. Monitor patients closely for need of emergency cardiorespiratory support. (5.2)

• Gadolinium is retained for months or years in brain, bone, and other organs. (5.3)

---------- ADVERSE REACTIONS ----------

The most frequent (≥0.2%) adverse reactions in clinical studies were nausea, headache, injection site pain, injection site coldness, and rash. (6.1)

Section 8 USE IN SPECIFIC POPULATIONS, the *Pediatric Use* subsection includes the following information *(excerpted):*

> No cases of NSF associated with Dotarem or any other GBCA have been identified in pediatric patients age 6 years and younger [see *Warnings and Precautions (5.1)*].
>
> (See aforementioned summary for safety and efficacy in patients in pediatric patients including term neonates)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of Search	March 1, 2019
Time Period of Search	April 01, 2015† - February 28, 2019
Search Type	FBIS Quick Query, Product-Manufacturer Reporting Summary
Product Terms	Product Active Ingredient- gadoterate meglumine Product name- Dotarem
MedDRA Search Terms (Version 21.1)	All PT terms

* See **Appendix A** for a description of the FAERS database.
† The most recent OSE Pediatric Postmarketing Pharmacovigilance and Drug Use review used search dates of March 20, 2013 through March 31, 2015. Therefore, this date was used to inform the start date of the search for this review.

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from April 1, 2015 through February 28, 2019 with gadoterate meglumine.

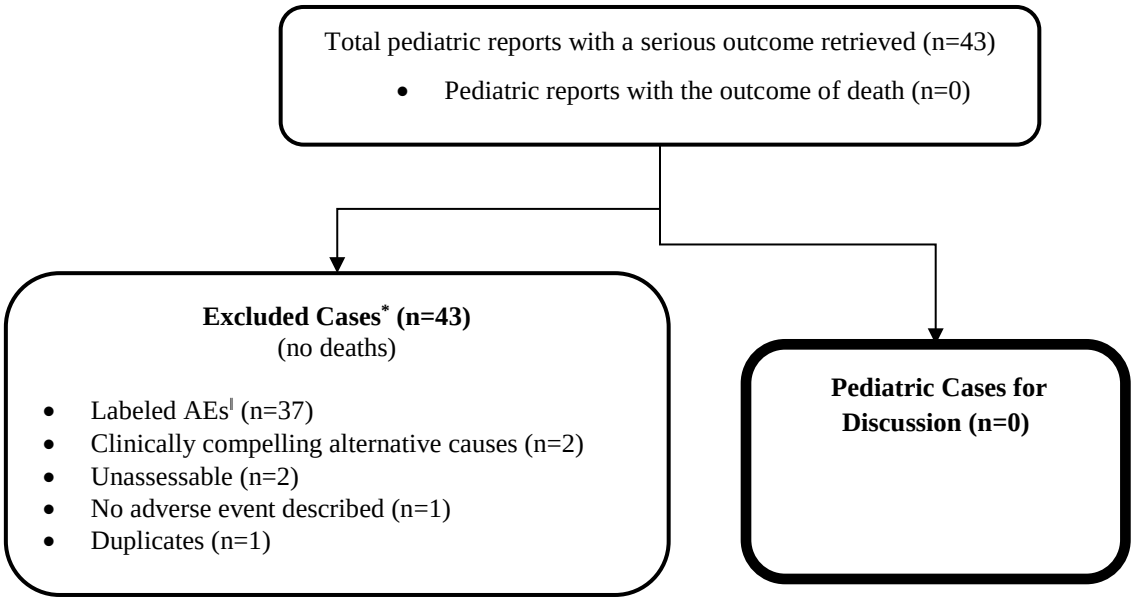
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from April 1, 2015 through February 28, 2019 with Gadoterate Meglumine			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	916 (394)	649 (131)	**9 (2)**
Pediatrics (0 - <17 years)	58 (24)	**43 (9)**	**0 (0)**

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 43 serious pediatric reports from April 1, 2015 through February 28, 2019. We reviewed all FAERS pediatric reports with a serious outcome. We did not identify any fatal pediatric AE reports. After reviewing the reports, we excluded all 43. See **Appendix B** for a line listing of the 43 excluded cases. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Gadoterate Meglumine



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

The main reason for exclusion was that 37 cases contained labeled AEs[a] including hypersensitivity (n=35), nausea (n=2), and dizziness and malaise (n=1). Hypersensitivity and anaphylactic reaction are labeled events in Dotarem labeling under Warnings and Precautions, and Adverse Reactions sections. Nausea, dizziness and malaise are labeled AEs in Dotarem labeling under the Adverse Reactions section. The reports are not unusual in number and we did not see any change in severity.

Two cases described clinically compelling alternative causes and provided insufficient information to assess if AEs were gadoterate meglumine related. One of the cases described a 13-year-old female with a medical history notable for lupus with renal complications, anemia, and thrombocytopenia who was hospitalized for staphylococcal sepsis and developed angioedema with acute pulmonary edema following administration of gadoterate meglumine with concomitant exposures to enalapril, "antibiotics", albumin, and a blood transfusion. The case lacked additional detail to determine if the AE was related to gadoterate meglumine or albumin, which is labeled for angioedema and hypersensitivity, or if it represented a transfusion reaction. The remaining case described a 4-year-old male with a history of prematurity who was hospitalized for suspected meningoencephalitis and developed fever, diarrhea, coma, renal

[a] One case may report more than one AE.

failure, and hepatic failure on the same day after gadoterate meglumine administration. Concomitant medications included chloral hydrate, cefotaxime, and acyclovir. The case lacked additional detail to assess if AEs were drug related or a sequelae of underlying disease process.

The remaining four cases were excluded because they contained insufficient information for assessment (n=2), reported no AE (n=1), or were duplicate reports (n=1).

4 DISCUSSION

We reviewed all serious FAERS reports with gadoterate meglumine in pediatric patients through age 16 years from April 1, 2015 through February 28, 2019. We chose this start date to capture all reports from the data lock date of a previous OSE review.

Our FAERS search retrieved 43 reports. This review focused on serious unlabeled adverse events (AEs) associated with gadoterate meglumine in pediatric patients. We did not identify any deaths associated with gadoterate meglumine. After reviewing the reports, we excluded all 43 because they described AEs that are well labeled (e.g., hypersensitivity, nausea, and dizziness with malaise), described AEs with compelling alternative etiologies, had limited information, did not describe an AE, or were duplicate reports.

We did not identify any new safety signals or apparent increased severity of any labeled AEs associated with gadoterate meglumine.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for gadoterate meglumine with this review.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all AEs associated with the use of gadoterate meglumine.

7 REFERENCES

1. Phelan K. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. In. *Dotarem.* http://wayback.archive-it.org/7993/20180127092521/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM461753.pdf: U.S.Food & Drug Administration. Briefing Materials for the September 16, 2015 Meeting of the Pediatric Advisory (Page 1 of 2); August 12, 2015.
2. Williams G. Cross-Discipline Team Leader Review. In. *Dotarem (gadoterate meglumine) Injection*. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM446880.pdf: U.S. Food & Drug Administrration. Reviews of Pediatric Studies Conducted under BPCA and PREA from 2012 – present; August 24, 2017.
3. Ma L. Clinical Pharmacology Review. In. *Dotarem (gadoterate meglumine) Injection- NDA 204781*. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM446881.pdf: U.S. Food & Drug Administration. Reviews of Pediatric Studies Conducted under BPCA and PREA from 2012 – present; August 4, 2017.
4. [Prescribing Information] Dotarem. In. Princeton, NJ: Guerbet; November 2018.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population

8.2 APPENDIX B. FAERS LINE LISTING OF THE EXCLUDED PEDIATRIC CASES (N=43)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1.	8/25/2015	11417723	1	US-GUERBET LLC-1041359	Non- Expedited	2	Male	U.S.	HO,LT,OT
2.	1/18/2016	11925382	2	US-GUERBET LLC-1046583	Expedited (15-Day)	11	Male	U.S.	HO
3.	3/28/2016	12214390	2	US-GUERBET LLC-1049790	Expedited (15-Day)	8	Female	U.S.	HO,LT
4.	8/11/2016	12644338	1	US-GUERBET LLC-1056196	Non- Expedited	16	Female	U.S.	OT
5.	11/14/2016	12936958	1	US-GUERBET LLC-1059496	Expedited (15-Day)	15	Female	U.S.	HO
6.	4/14/2017	13444819	2	US-GUERBET-US-20170065	Expedited (15-Day)	5	Female	U.S.	HO
7.	12/14/2017	14283959	1	US-GUERBET-US-20170245	Non- Expedited	16	Female	U.S.	HO
8.	3/2/2018	14590814	1	US-GUERBET-US-20180052	Expedited (15-Day)	12	Female	U.S.	OT
9.	11/20/2018	15640853	1	US-GUERBET-US-20180286	Non- Expedited	12	Female	U.S.	HO
10.	5/5/2015	11096033	2	TR-20150003	Expedited (15-Day)	14	Male	TUR	HO,LT
11.	8/14/2018	15277533	1	NZ-GUERBET-NZ-20180030	Expedited (15-Day)	11	Male	NZL	OT
12.	12/19/2015	11854102	1	MY-GUERBET LLC-1045706	Expedited (15-Day)	16	Male	MYS	OT
13.	12/31/2015	11882175	1	JP-GUERBET LLC-1046026	Expedited (15-Day)	10	Female	JPN	HO
14.	5/4/2016	12335247	2	JP-GUERBET LLC-1051440	Expedited (15-Day)	4	Male	JPN	HO
15.	12/22/2017	14317381	1	IT-GUERBET-IT-20170189	Expedited (15-Day)	16	Female	ITA	OT
16.	9/25/2018	15426094	1	IT-GUERBET-IT-20180163	Expedited (15-Day)	13	Null	ITA	HO
17.	10/15/2018	15499441	1	IE-GUERBET-IE-20180030	Expedited (15-Day)	15	Female	IRL	HO,LT
18.	3/6/2018	14603238	1	GR-GUERBET-GR-20180005	Expedited (15-Day)	14	Male	GRC	HO,OT
19.	3/23/2017	13362797	1	GB-GUERBET LLC-1064554	Expedited (15-Day)	16	Female	GBR	OT
20.	3/29/2018	14693702	4	GB-GUERBET-GB-20180052	Expedited (15-Day)	13	Female	GBR	HO
21.	8/17/2015	11388113	1	FR-GUERBET LLC-1041137	Expedited (15-Day)	13	Female	FRA	HO,OT
22.	10/30/2015	11686468	1	FR-GUERBET LLC-1043588	Expedited (15-Day)	9	Male	FRA	HO
23.	4/20/2016	12286158	1	FR-GUERBET LLC-1050756	Expedited (15-Day)	4	Male	FRA	HO
24.	1/30/2017	13162612	1	FR-GUERBET LLC-1062491	Expedited (15-Day)	11	Female	FRA	HO
25.	8/4/2017	13833266	1	FR-GUERBET-FR-20170422	Expedited (15-Day)	14	Female	FRA	HO
26.	4/17/2018	14768606	2	FR-GUERBET-FR-20180208	Expedited (15-Day)	5	Female	FRA	HO
27.	6/4/2018	14970457	1	FR-GUERBET-FR-20180297	Expedited (15-Day)	7	Female	FRA	OT
28.	6/22/2018	15051415	1	FR-GUERBET-FR-20180325	Non- Expedited	5	Null	FRA	OT
29.	7/2/2018	15098164	2	FR-GUERBET-FR-20180357	Non- Expedited	4	Male	FRA	HO,LT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
30.	10/9/2018	15479812	1	FR-GUERBET-FR-20180523	Non- Expedited	14	Male	FRA	HO,LT,OT
31.	3/10/2017	13319668	2	FI-GUERBET LLC-1064101	Expedited (15-Day)	15	Male	FIN	HO
32.	10/30/2017	14143138	1	FI-GUERBET-FI-20170017	Non- Expedited	7	Female	FIN	HO
33.	11/9/2017	14174136	1	FI-GUERBET-FI-20170020	Expedited (15-Day)	8	Female	FIN	HO
34.	3/23/2016	12204974	1	DE-GUERBET LLC-1049505	Expedited (15-Day)	4	Female	DEU	LT
35.	1/3/2018	14345838	1	DE-GUERBET-DE-20170154	Expedited (15-Day)	15	Female	DEU	OT
36.	3/22/2018	14671048	1	DE-GUERBET-DE-20180033	Expedited (15-Day)	14	Female	DEU	OT
37.	12/16/2016	13034614	1	CO-GUERBET LLC-1060898	Expedited (15-Day)	4	Female	COL	OT
38.	12/2/2016	12994854	1	CH-GUERBET LLC-1060340	Expedited (15-Day)	9	Female	CHE	OT
39.	10/8/2015	11611474	1	BR-GUERBET LLC-1042723	Expedited (15-Day)	11	Female	BRA	HO
40.	10/12/2015	11619810	1	BR-GUERBET LLC-1042817	Expedited (15-Day)	11	Female	BRA	OT
41.	8/8/2016	12634924	1	AT-GUERBET LLC-1056036	Expedited (15-Day)	3	Male	AUT	OT
42.	4/17/2018	14768466	1	AU-GUERBET-AU-20180009	Expedited (15-Day)	9	Female	AUS	OT
43.	5/11/2017	13537262	1	AR-GUERBET-AR-20170003	Expedited (15-Day)	15	Male	ARG	HO,LT

***As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.**

Abbreviations: HO=Hospitalization, LT= Life-threatening, OT=Other medically significant
TUR= Turkey, NZL=New Zealand, MYS=Malaysia, JPN=Japan, ITA=Italy, IRL=Ireland, GRC=Greece, GBR=United Kingdom, FRA=France, FIN=Finland, DEU=Germany, COL=Colombia, BRA=Brazil, AUT=Austria, AUS=Australia, ARG=Argentina

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IDA-LINA DIAK
06/11/2019 10:47:25 AM