Office of Clinical Pharmacology Review

NDA Number	**22-287 / SDN 1226; SDN 1256; SDN 1279**
Submission Date	09/30/2015;12/02/2015; 03/24/2016
Submission Type	Pediatric Efficacy Supplement (S-021, S-022, S-023)
Brand Name	Dexilant
Generic Name	Dexlansoprazole
Reviewer	Shen Li, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products
Applicant	Takeda Pharmaceuticals USA Inc.
Formulation and Strength	Delayed-Release Capsule: 30 mg and 60 mg
Proposed Regimen	Approved Dosage in Adults: • Healing of EE: 60 mg once daily for up to 8 weeks. • Maintenance of healed EE: 30 mg once daily for up to 6 months (in adults). • Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks. *The Applicant proposed to add: "30 mg once daily for up to 4 months in adolescents 12 years of age and older" for Maintenance of healed EE.*
Proposed Indication	Same as the Approved Indications in Adults: • Healing of all grades of erosive esophagitis (EE). • Maintaining healing of EE and relief of heartburn. • Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

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1 Executive Summary

Dexlansoprazole is a proton pump inhibitor, the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers). Dexilant (dexlansoprazole) delayed-release capsules were approved for adults in 2009, indicated for healing of all grades of erosive esophagitis (EE), maintaining healing of EE and relief of heartburn, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

In this application, the Applicant proposes the use of Dexilant delayed-release capsules in pediatric patients aged 12 to 17 years, with the same indications as approved in adult patients. The proposed pediatric dosage regimens are:

- Healing of EE: 60 mg once daily for up to 8 weeks.
- Maintenance of healed EE: 30 mg once daily for up to 4 months.
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks.

In support of the proposed indications, three clinical trials in pediatric patients aged 12 to 17 years were conducted: 1) a phase 1, randomized, open-label study to evaluate the pharmacokinetics and safety of dexlansoprazole 30 or 60 mg once daily (QD) for 7 days in adolescents with symptomatic non-erosive GERD; .2) an open-label, 4-week study to evaluate the safety and effectiveness of dexlansoprazole 30 mg QD in adolescents with symptomatic non-erosive GERD; and 3) a study to evaluate the safety and effectiveness of dexlansoprazole 60 mg QD for healing of EE (open-label) and dexlansoprazole 30 mg QD for maintenance of healed EE (placebo-controlled) in adolescents with EE. The studies were conducted to fulfill the following Pediatric Research Equity Act (PREA) Post-Marketing Requirements as below:

- PMR 1788-1: Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients 12 years to 17 years of age.
- PMR 1356-5: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.

This review is focused on the pharmacokinetics of dexlansoprazole in pediatric patients aged 12 to 17 years.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this NDA submission and found it acceptable from a clinical pharmacology standpoint provided that a mutually satisfactory agreement can be reached between the Applicant and Agency regarding the labeling language. As such, the Applicant has fulfilled the requirements on the pharmacokinetics evaluation in patients 12-17 years of age, which is a part of PMR 1788-1.

1.2 Post-Marketing Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

In Study T-P107-163 entitled "A Phase 1, Randomized, Open-Label, Parallel Group, Multicenter Study to Evaluate the Pharmacokinetics and Safety of Dexlansoprazole Modified Release Capsules (30 mg and 60 mg) in Adolescents with Symptomatic Gastroesophageal Reflux Disease", 36 pediatric patients aged 12 to 17 years received dexlansoprazole delayed release capsules 30 or 60 mg once daily for 7 days.

Pharmacokinetics of Dexlansoprazole in Adolescent Patients

- Similar to the PK concentration-time profiles observed in adults, plasma concentrations of dexlansoprazole displayed 2 distinct peaks, reflective of the release characteristics of the two granule types contained in the dexlansoprazole capsule. Systematic exposure of dexlansoprazole increased approximately dose proportionally from 30 mg to 60 mg in adolescent patient, similar to that observed in adult patients. A summary of plasma PK parameters of dexlansoprazole in pediatric patients 12 to 17 years of age is presented in Table 1.

Table 1: Summary of plasma pharmacokinetic parameters of dexlansoprazole in patients 12 to 17 years of age.

	Tmax (hr)	Cmax (ng/mL)	Cmax/Dose (ng/mL/mg)	AUC(0-tau) (ng·hr/mL)	AUC(0-tau)/ Dose (ng·hr/mL/mg)	T1/2(a) (hr)	CL/F (L/hr)
Regimen A: Multiple 30 mg Dose – Subjects Age 12-17 years – Day 7							
N	17	17	17	16	16	16	16
Mean	4.65	691	23.0	2886	96.21	1.66 [1.32]	12.8
SD	2.909	367.5	12.25	1355.2	45.173	0.871	6.09
Min	1.00	255	8.50	1204	40.12	0.63	5.2
Median	5.00	609	20.30	2520	83.99	1.43	11.9
Max	12.00	1600	53.33	5741	191.36	3.74	24.9
%CV	63	53	53	47	47	52	48
Regimen B: Multiple 60 mg Dose – Subjects Age 12-17 years – Day 7							
N	18	18	18	18	18	18	18
Mean	3.31	1136	18.9	5120	85.3	2.59 [2.04]	15.3
SD	1.519	582.2	9.70	2986.5	49.77	1.379	7.52
Min	1.00	399	6.65	1996	33.27	0.95	4.9
Median	3.50	1045	17.42	4124	68.73	2.36	14.57
Max	6.03	2620	43.67	12246	204.10	6.30	30.05
%CV	46	51	51	58	58	53	49

(a) Harmonic mean is shown in brackets.

Comparison of Pharmacokinetics between Adolescent Patients and Adults

Systemic exposures for dexlansoprazole in adolescent patients who received dexlansoprazole 30 and 60 mg capsules were similar to those in healthy adults or adult patients. The details are given below.

Adolescent patients vs. healthy adults: Following oral administration of dexlansoprazole 30 mg QD, mean (%CV) Cmax and AUC(0-tau) at steady state in adolescent patients were 691 (53%) ng/mL and 2886 (47%) ng.h/mL, respectively, and were 658 (40%)

ng/mL and 3275 (47%) ng.h/mL, respectively in healthy adults. For the 60 mg QD dose, mean Cmax and AUC(0-tau) at steady state in adolescent patients were 1136 (51%) ng/mL and 5120 (58%) ng.h/mL, respectively, and were 1397 (51%) ng/mL and 6529 (60%) ng.h/mL, respectively, in healthy adults. The mean PK parameters are presented in Table 2.

Adolescent patients vs. adult patients: In one study (Study T-P105-129) with adult patients mean systemic exposures for dexlansoprazole appeared higher than the mean values in adolescent patients. However, based on the review of individual PK data, the higher mean exposures in adult patients were due to two patients with particularly high exposures. The reason for the higher exposure in those two adult patients is unknown; potentially concomitant medications that are CYP2C19 inhibitors can cause drug interactions resulting in higher systemic exposures. Overall, individual Cmax and AUC values in adolescent patients were similar to those observed in the rest of adult patients.

Table 2: Dexlansoprazole pharmacokinetic parameters for patients 12 to 17 years of age and healthy adults following multiple daily 30 or 60 mg oral doses of dexlansoprazole capsules.

	N	t_{max} (hr)	C_{max} (ng/mL)	AUC_{24} or AUC_{τ} (a) (ng·hr/mL)	$t_{1/2z}$ (hr)	CL/F (L/hr)
Multiple 30 mg Dose – Adolescent GERD Subjects – Day 7 Data						
Mean	17 (b)	4.65	691	2886	1.66	12.8
%CV		63	53	47	52	48
Multiple 30 mg Dose – Healthy Adult Subjects – Day 5 Data						
Mean	44 (c)	4.45	658	3275	1.75	11.4
%CV		37	40	47	49	48
Multiple 60 mg Dose – Adolescent GERD Subjects – Day 7 Data						
Mean	18	3.31	1136	5120	2.59	15.3
%CV		46	51	58	53	49
Multiple 60 mg Dose – Healthy Adult Subjects – Day 5 Data						
Mean	79 (d)	4.64	1397	6529	1.83	11.6
%CV		46	51	60	52	46

(a) AUC_{24} for healthy adults and AUC_{tau} for pediatric patients 12 to 17 years of age (tau was 24 hours in pediatric study).
(b) N=16 for AUCtau, t1/2z, and CL/F.
(c) N=43 for AUC_{24}, t1/2z, and CL/F.
(d) N=73 for AUC_{24} and t1/2z; N=41 for CL/F.

2 Question-Based Review

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Dexlansoprazole is the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers). Dexlansoprazole delayed-release capsules (Dexilant) were approved in adults on 01/30/2009 for treatment of:

- Healing of all grades of erosive esophagitis (EE).
- Maintaining healing of EE and relief of heartburn.
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

Approved dosage in adults:

- Healing of EE: 60 mg once daily for up to 8 weeks.
- Maintenance of healed EE: 30 mg once daily for up to 6 months.
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks.

In this efficacy supplement, the Applicant proposes to fulfill two PREA Post-Marketing Requirements as below:

- PMR 1788-1: Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients 12 years to 17 years of age.
- PMR 1356-5: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.

This NDA submission included the following three studies:

- Study T-P107-163: a phase 1, randomized, open-label, parallel-groupstudy to evaluate the pharmacokinetics and safety of dexlansoprazole 30 or 60 mg once daily (QD) in 36 adolescents with symptomatic GERD.
- Study TAK-390MR_206: an open-label, 4-week study to evaluate the safety and effectiveness of dexlansoprazole 30 mg QD in 104 adolescents with symptomatic non-erosive GERD.
- Study TAK-390MR_207: a 36-week study designed to evaluate the safety and effectiveness of dexlansoprazole 60 mg QD for healing of EE (open-label) and dexlansoprazole 30 mg QD for maintenance of healed EE (placebo-controlled) in 62 adolescents with EE.

2.1.2 What is the formulation of the drug product used in pediatric studies?

The approved Dexilant delayed-release capsules for adult patients contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-

dependent dissolution profiles. Dexilant is available in two dosage strengths: 30 mg and 60 mg, per capsule. The same formulation was used in pediatric studies.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Dexlansoprazole is a proton pump inhibitor, a compound that inhibits gastric acid secretion. The proposed pediatric indications are the same as approved in adults:

- Healing of all grades of erosive esophagitis (EE).
- Maintaining healing of EE and relief of heartburn.
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed oral dosage for patients aged 12 to 17 years old are:

- Healing of EE: 60 mg once daily for up to 8 weeks.
- Maintenance of healed EE: 30 mg once daily for up to 4 months in adolescents 12 years of age and older.
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

For the design features of the clinical trials, please see Table 3.

Table 3: Overview of clinical trials in adolescent patients.

Study No. No. of Centers-Country Study Start–End Dates	Study Design Primary Objective (Endpoint)	Population (a) and Type (criteria) Gender and Race (n[%]) (b) Mean Age (min-max)	Treatment Duration	Treatment (c) (Dosed/Completed)
5.3.3.2 Patient PK and Initial Tolerability Studies				
T-P107-163 3-United States 31 May 09 to 10 Sep 09	Randomized, open-label, multicenter, multiple dose, parallel-group PK, safety	36 adolescents with GERD; 18 subjects per group 14 (39%) Men, 22 (61%) Women 28 (78%) W, 8 (22%) B 14.6 (12-17) years	7 days	Capsule, 30 mg (18/18) or 60 mg (18/18)
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication				
TAK-390MR_207 8-United States, 6-Poland, 3-Portugal, 1-Mexico 22 Jun 12 to 10 Nov 14	Healing: open-label, multicenter, multiple-dose, noncomparative Maintenance: randomized, double-blind, multicenter, multiple-dose, parallel-group, placebo-controlled Efficacy (healing of EE/maintenace of healed EE), safety	Healing: 62 adolescents with EE 38 (61%) Men, 24 (39%) Women 61 (98%) W, 1 (2%) B 14.8 (12-17) years Maintenance: 51 subjects with healed EE 30 (59%) Men, 21 (41%) Women 50 (98%) W, 1 (2%) B 14.7 (12-17) years	Healing: 8 weeks Maintenance: 16 weeks Follow-up: 12 weeks	Healing: capsule, 60 mg (62/58) Maintenance: capsule, 30 mg (25/18), or placebo (26/20)
5.3.5.2 Study Reports of Uncontrolled Clinical Studies				
TAK-390MR_206 19-United States, 4-Hungary, 4-Poland, 4-Portugal, 2-Mexico, 1-Belgium, 1-Brazil, 1-Italy 22 Jun 12 to 14 Jan 14	Open-label, multicenter, multiple-dose, noncomparative Efficacy (symptomatic GERD), safety	104 adolescents with symptomatic nonerosive GERD 31 (30%) Men, 73 (70%) Women 95 (91%) W, 6 (6%) B, 3 (3%) M 15 (12-17) years	4 weeks	Capsule, 30 mg (104/102)

EE=erosive esophagitis, GERD=gastroesophageal reflux disease, PK=pharmacokinetics.
(a) Population=number of subjects who received at least 1 dose of study medication.
(b) Races: A=Asian, B=Black, M=Multiracial, O=Other, W=White.
(c) Once-daily tablets by oral administration unless otherwise noted.
(d) Median values are given.

2.2.2 What is the clinical endpoint for efficacy?

In the open-label trial (Study TAK-390MR_206), dexlansoprazole 30 mg QD was administered in adolescent patients with symptomatic non-erosive GERD for 4 weeks. Efficacy was evaluated using the percentage of days with neither daytime nor nighttime heartburn over the 4 weeks of treatment.

Study TAK-390MR_207 contained an open-label healing phase (treatment with dexlansoprazole 60 mg QD for 8 weeks for healing of EE), and a double-blind, placebo-controlled maintenance phase (treatment with dexlansoprazole 30 mg QD for 16 weeks for maintenance of healed EE) in adolescent patients. Efficacy was evaluated using the following endpoints:

- The percentage of patients with healing of EE by Week 8.
- The percentage of patients who maintained healing of EE from Week 8 to Week 24 among the patients who were healed at Week 8.
- The percentage of days with neither daytime nor nighttime heartburn over the first 8 weeks of treatment.
- The percentage of days with neither daytime nor nighttime heartburn over Weeks 8 to 24 among the patients who were healed at Week 8.

2.2.3 Is dexlansoprazole in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Please see Section 2.3 for more details.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the clinical trial design features and efficacy outcome?

The efficacy of dexlansoprazole for the treatment of symptomatic non-erosive GERD was assessed with one dose level, i.e., dexlansoprazole 30 mg QD for 4 weeks (Study TAK-390MR_206). Effectiveness of treatment was evaluated via the percentage of days with neither daytime nor nighttime heartburn over the 4 weeks of treatment (Table 4).

Table 4: Patient-Rated 24-Hour Heartburn Assessment in Patients with Symptomatic Non-erosive GERD in Study TAK-390MR_206.

	Dexlansoprazole 30 mg QD N=104		
	Mean (SD)	**Median**	**Range**
Percentage of days with neither daytime nor nighttime heartburn	47.1 (32.18)	47.3	0-100

Source: Applicant's report, Clinical Overview, Table 4a on page 13.

In Study TAK-390MR_207, the efficacy for healing of EE was evaluated with dexlansoprazole 60 mg QD for 8 weeks, and the efficacy for maintenance of healed EE was evaluated with dexlansoprazole 30 mg QD for 16 weeks in adolescent patients. At the end of 8 weeks of treatment, 87.9% of the patients were healed (Table 5). After 16 weeks of treatment with dexlansoprazole 30 mg QD, 81.8% of adolescent patients had maintained healing of EE, compared to 58.3% of the adolescent patients who had received placebo had maintained healing of EE (Table 6).

Table 5: Crude Healing Rates of EE by Week 8 in Study TAK-390MR_207.

	Dexlansoprazole 60 mg QD		
Week 8 Endoscopy Result	**N**	**n (%) (a)**	**[95% CI] (b)**
Healed	58	51 (87.9)	[76.7, 95.0]

Source: Applicant's report, Clinical Overview, Table 4c on page 14.

Table 6: Crude Rates for Maintenance of Healing of EE in Study TAK-390MR_207.

	Placebo N=26			Dexlansoprazole 30 mg QD N=25		
Week 24 Endoscopy Result	**N**	**n (%) (a)**	**[95% CI] (b)**	**N**	**n (%) (a)**	**[95% CI] (b)**
Maintained	24	14 (58.3)	[36.6, 77.9]	22	18 (81.8)	[59.7, 94.8]

Source: Applicant's report, Clinical Overview, Table 4e on page 15.

The PK blood samples were not collected in these two pediatric efficacy studies. As such, the oncentration-response relationship for efficacy was not assessed in pediatric patients. The detailed review for the efficacy of dexlansoprazole is deferred to the clinical reviewers and biostatistics reviewers.

Reviewer's comments:
Efficacy for healing of EE and treating symptomatic non-erosive GERD were evaluated in uncontrolled, open-label studies. The review of acceptability for the uncontrolled, open-label efficacy evaluation in this submission is deferred to the clinical reviewers.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

In pharmacokinetic study T-P107-163, 36 pediatric patients were randomly assigned in equal numbers to receive dexlansoprazole 30 mg or 60 mg QD for 7 days. All 36 patients completed the study after receiving all 7 doses. Overall, 12 of 36 patients experienced a total of 21 TEAEs during the 7-day study; this included 38.9% of patients who received dexlansoprazole 30 mg and 27.8% of patients who received dexlansoprazole 60 mg (Table 7).

Table 7: TEAEs reported by ≥2 total patients in Study T-P107-163.

MedDRA SOC MedDRA PT (a)	Dose Group Dexlansoprazole 30 mg QD N=18		Dexlansoprazole 60 mg QD N=18		Total N=36	
	n	(%)	n	(%)	n	(%)
Any event	7	(38.9)	5	(27.8)	12	(33.3)
Gastrointestinal disorders						
Abdominal pain	4	(22.2)	0		4	(11.1)
Vomiting (b)	0		2	(11.1)	2	(5.6)
Nervous system disorders						
Headache	1	(5.6)	2	(11.1)	3	(8.3)
Dizziness	1	(5.6)	1	(5.6)	2	(5.6)
Presyncope (c)	1	(5.6)	1	(5.6)	2	(5.6)

Reviewer's comment:
While the sample size is limited in both treatment groups, no apparent exposure-response relationship for TEAEs was observed in pediatric patients following dexlansoprazole 30 mg or 60 mg QD for 7 days. The review of safety profile is deferred to clinical reviewers.

2.2.4.3 Are there any unresolved dosing or administration issues?

Proposed dosage in adolescent patients 12 – 17 years of age:
- Healing of EE: 60 mg once daily for up to 8 weeks.
- Maintenance of healed EE: 30 mg once daily for up to 4 months.
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks.

For healing of EE and symptomatic non-erosive GERD, the proposed dosage in adolescent patients is the same as the approved dosage for adult patients.

For maintenance of healed EE, the proposed dose and dosing frequency (i.e., 30 mg once daily) are the same as the approved dosage for adult patients, but the proposed duration of treatment is up to 4 months in adolescent patients, which is different from that for adult patients (i.e., up to 6 months).

Reviewer's comments:
- ***Effectiveness of dexlansoprazole for maintenance of healed EE in adolescent patients was evaluated in Study TAK-390MR_207 using the proposed dosage (i.e., 30 mg once daily for up to 4 months).***
- ***The review of acceptability for the proposed dosage in adolescent patients in this submission is deferred to the clinical reviewers.***

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK parameters in pediatric patients?

Following daily administration of dexlansoprazole delayed release capsules 30 or 60 mg for 7 days to pediatric patients 12 to 17 years of age, plasma concentrations of dexlansoprazole displayed 2 distinct peaks, reflective of the release characteristics of the two granule types contained in the dexlansoprazole capsule, and were similar to the PK profiles observed in adults.

Table 8: Summary of plasma pharmacokinetic parameters of dexlansoprazole in pediatric patients 12 to 17 years of age.

	Tmax (hr)	Cmax (ng/mL)	Cmax/Dose (ng/mL/mg)	AUC(0-tau) (ng·hr/mL)	AUC(0-tau)/ Dose (ng·hr/mL/mg)	T1/2(a) (hr)	CL/F (L/hr)
Regimen A: Multiple 30 mg Dose – Subjects Age 12-17 years – Day 7							
N	17	17	17	16	16	16	16
Mean	4.65	691	23.0	2886	96.21	1.66 [1.32]	12.8
SD	2.909	367.5	12.25	1355.2	45.173	0.871	6.09
Min	1.00	255	8.50	1204	40.12	0.63	5.2
Median	5.00	609	20.30	2520	83.99	1.43	11.9
Max	12.00	1600	53.33	5741	191.36	3.74	24.9
%CV	63	53	53	47	47	52	48
Regimen B: Multiple 60 mg Dose – Subjects Age 12-17 years – Day 7							
N	18	18	18	18	18	18	18
Mean	3.31	1136	18.9	5120	85.3	2.59 [2.04]	15.3
SD	1.519	582.2	9.70	2986.5	49.77	1.379	7.52
Min	1.00	399	6.65	1996	33.27	0.95	4.9
Median	3.50	1045	17.42	4124	68.73	2.36	14.57
Max	6.03	2620	43.67	12246	204.10	6.30	30.05
%CV	46	51	51	58	58	53	49

(a) Harmonic mean is shown in brackets.

The point estimates show that the dose normalized AUCs and Cmax for the 30 mg dexlansoprazole capsule are about 16% to 21% higher than those for the 60 mg (see Table 9).

Table 9: Statistical analysis of dose proportionality of dexlansoprazole in adolescent patients.

Parameter	Point Estimate	90% Confidence Interval
30 mg (Test) versus 60 mg (Reference) Dexlansoprazole Capsule		
Cmax/dose	1.210	0.897 – 1.630
AUC(0-tlqc)/dose	1.158	0.864 – 1.551
AUC(0-tau)/dose	1.168	0.864 – 1.579

Reviewer's comments:

- ***At the time that Study T-P107-163 was performed, PK characteristics of dexlansoprazole for the delayed-release formulation in pediatric patients were unknown. As such, a conservative approach was used by the Applicant to exclude patients who were poor metabolizers in order to reduce the risk of a pediatric patient potentially being exposed to very high plasma concentrations in this first dexlansoprazole study in the pediatric population. This approach is***

acceptable. Additionally, the Applicant stated (see Applicant's Response to Clinical Pharmacology Information Request, dated on 11/16/2015) that of the 61 patients who were screened for metabolizer status in Study T-P107-163, 44 patients were homozygous EMs, 16 were heterozygous EMs, and only 1 was determined to be a PM.

- ***Overall, systematic exposure of dexlansoprazole appeared approximately dose proportional from 30 mg to 60 mg in adolescent patients.***

2.2.5.2 Were pediatric PK parameters and adult PK parameters similar?

Yes. Systemic exposures for dexlansoprazole in adolescent patients who received dexlansoprazole 30 and 60 mg capsules were similar to those in healthy adults or adult patients. The details are given below.

Adolescent patients vs. healthy adults: Following oral administration of dexlansoprazole 30 mg QD, mean (CV%) Cmax and AUC(0-tau) at steady state in adolescent patients were 691 (53%) ng/mL and 2886 (47%) ng.h/mL, respectively, and were 658 (40%) ng/mL and 3275 (47%) ng.h/mL, respectively in healthy adults. For the 60 mg QD dose, mean Cmax and AUC(0-tau) at steady state in adolescent patients were 1136 (51%) ng/mL and 5120 (58%) ng.h/mL, respectively, and were 1397 (51%) ng/mL and 6529 (60%) ng.h/mL, respectively, in healthy adults. The mean PK parameters are presented in Table 2.

Adolescent patients vs. adult patients: In one study (Study T-P105-129) with adult patients mean systemic exposures for dexlansoprazole appeared higher than the mean values in adolescent patients. However, based on the review of individual PK data, the higher mean exposures in adult patients were due to two patients with particularly high exposures. The reason for the higher exposure in those two adult patients is unknown; potentially concomitant medications that are CYP2C19 inhibitors can cause drug interactions resulting in higher systemic exposures. Overall, individual Cmax and AUC values in adolescent patients were similar to those observed in the rest of adult patients.

2.3 Analytical Section

2.3.1 How is dexlansoprazole identified and measured in the plasma in the clinical pharmacology?

Bioanalytical analysis of dexlansoprazole in the plasma samples was performed at (b) (4) Plasma samples were stored frozen at -20^{o}C or colder until analysis. The method validation report titled "Quantitation of Lansoprazole in Human Plasma via HPLC with MS/MS Detection (Report P896)" and the bioanalytical report for Study T-P107-163 were submitted. Previous Clinical Pharmacology Review for NDA 022-287 (dated 12/03/2008) indicated that no bioinversion from dexlansoprazole (the R-(+)-enantiomer) to the S-(-)-enantiomer of lansoprazole.

Briefly, samples were are extracted by solid phase extraction and plasma dexlansoprazole concentrations were measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with lansoprazole-d_4 as an internal standard. The assay method had a lower limit of quantification of 2.00 ng/mL using 20 μL of plasma.

2.3.2 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What are the accuracy, precision and selectivity at these limits?

Assay validation calibration standard curve consisted of 8 levels ranged from 2.00 to 2000 ng/mL in human plasma, and was calculated using a linear-weighted, 1/concentration², least-squares regression algorithm. The R^2 ranged between 0.9989 and 0.9996. Precision (% CV) for the calibration standards ranged from 1.03% to 7.04%, while accuracy (% Bias) ranged from -1.84% to 1.33%. Stability in human plasma was demonstrated to be 24.75 hours at room temperature and 112 days at -20 ºC. Stability was shown up to three freeze-thaw cycles. No matrix interference was noted.

Calibration standard curve for this study T-P107-163 consisted of 8 levels ranged from 2.00 to 2000 ng/mL in human plasma, and the R^2 ranged between 0.9959 and 0.9991. Quality control samples at 5 different concentrations (6, 15, 60, 250, and 1500 ng/mL) were prepared, and the accuracy and the precision were within the acceptable limit. There were 54 samples (11% of a total of 492 analyzed samples) reanalyzed to test the reproducibility of the method. Acceptance criteria were met for incurred sample reanalysis as 96% (52 out of 54) of the repeat results and original results were within 20% of their mean value.

Reviewer's comments:
The bioanalytical method used to determine dexlansoprazole concentrations in this NDA is acceptable.

3 Labeling Recommendation

We recommend that the pharmacokinetic results as provided in the NDA supplement be reflected in the labeling Section 12.3 (Clinical Pharmacology/Pharmacokinetics).

Detailed edits for clinical pharmacology related information were conveyed to the Applicant and under negotiation as of this writing.

4 Appendices

4.1 OCP Filing Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	NDA 22287	**SDN**	1226
Applicant	Takeda Global Research & Development Center, Inc.	**Submission Date**	09/30/2015
Generic Name	Dexlansoprazole Delayed Release Capsules	**Brand Name**	Dexilant
Drug Class	Proton pump inhibitor (PPI)		
Indication	*Sponsor-proposed indications in pediatric patients 12 to 17 years of age (same as the approved indications in adults):* • Healing of all grades of erosive esophagitis (EE). • Maintaining healing of EE and relief of heartburn. • Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).		
Dosage Regimen	*Approved Dosage in Adults:* • Healing of EE: 60 mg once daily for up to 8 weeks. • Maintenance of healed EE: 30 mg once daily for up to 6 months (in adults). • Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks. • Hepatic impairment: Consider 30 mg maximum daily dose for patients with moderate hepatic impairment (Child-Pugh Class B). No studies were conducted in patients with severe hepatic impairment (Child-Pugh Class C). • DEXILANT can be taken without regard to food. *The sponsor proposed to add: "30 mg once daily for up to 4 months in adolescents 12 years of age and older" in the 2nd bullet point (for Maintenance of healed EE).*		
Dosage Form	Delayed-Release Capsule: 30 mg and 60 mg	**Route of Administration**	Oral
OCP Division	DCP 3	**OND Division**	DGIEP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
DCP3	Shen Li	Sue-Chih Lee	
Pharmacometrics	Not applicable		
Genomics	Not applicable		
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	11/27/2015	**74-Day Letter Date**	12/11/2015
Review Due Date	6/20/2016	**PDUFA Goal Date**	7/29/2016

Application Fileability
Is the Clinical Pharmacology section of the application fileable? ☑ Yes ☐ No If no list reason(s);
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? ☐ Yes ☑ No

If yes list comment(s) :

The following minor comments will be conveyed to the sponsor via Information Requests:

- Confirm whether the capsule formulation used in the pediatric studies is the to-be-marketed formulation.
- Explain the rationale for why CYP2C19 poor metabolizers were excluded from the pediatric PK study and clarify whether CYP2C19 poor metabolizers were also excluded from the adult PK data when comparing the PK profiles in pediatric subjects aged 12 to 17 years and healthy adult subjects. In addition, we recommend you also provide the comparison of PK profiles between pediatric subjects with gastroesophageal reflux disease (GERD) and adults with GERD (if available).
- Plasma PK samples were analyzed for lansoprazole per the bioanalytical report for Study T-P107-163. Explain why this method is appropriate for the quantification of dexlansoprazole.
- AUC(0-tau) was not reported for Subject 2003004 with a footnote that this parameter was not estimable. Explain the reason why AUC(0-tau) was not estimable for Subject 2003004.
- Additionally, Subject 2003005 was excluded from the PK analysis because most of the PK samples were not collected. Explain the reason for the missing PK samples of Subject 2003005.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain:

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	1	Multiple dose PK was evaluated in Study T-P107-163 in pediatric subjects 12 to 17 years of age with symptomatic GERD after once daily dosing of either 30 or 60 mg for 7 days

☐ Mass Balance Study		
☑ Other (e.g. dose proportionality)		Dose proportionality was evaluated in Study T-P107-163 for the 2 dose levels administered (30 and 60 mg QD for 7 days)
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	1
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	To confirm the capsule formulation used in the pediatric studies is the to-be-marketed formulation.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	The sponsor submitted one PK study (T-P107-163) conducted in pediatric subjects 12 to 17 years of age with symptomatic GERD.
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay	☑Yes ☐No ☐N/A	Plasma samples were analyzed for lansoprazole per the bioanalytical

for the moieties of interest?		report for Study T-P107-163.
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	PK analysis dataset only.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	Two dose levels (30 and 60 mg QD for 7 days) were evaluated in the PK study.
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to	☐Yes ☐No ☑N/A	CYP2C19 PMs were excluded from

use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		the pediatric PK study T-P107-163.
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
This is optional, discuss with your TL content and format

The sponsor submitted this NDA Supplement proposing to expand the adult indications for Dexilant (dexlansoprazole) delayed-release capsules to include pediatric patients 12 to 17 years of age.

Dexlansoprazole, the R-enantiomer of lansoprazole, is a proton pump inhibitor (PPI). Dexilant was approved by the Food and Drug Administration on 01/30/2009, for the treatment of healing of erosive esophagitis (EE), maintenance of healed EE and relief of heartburn, and symptomatic non-erosive gastroesophageal reflux disease (GERD) in adults.

Dexilant is available in a dual delayed-release formulation, containing 2 types of granules (with different pH-dependent release profile) within a single capsule. Dexilant capsules in 30 mg and 60 mg strengths are available for adult use. Directions for use in each indication for adults are summarized in the following table:

Table 1. DEXILANT Dosing Recommendations

Indication	Recommended Dose	Frequency
Healing of EE	60 mg	Once daily for up to 8 weeks
Maintenance of Healed EE and relief of heartburn	30 mg	Once daily*
Symptomatic Non-Erosive GERD	30 mg	Once daily for 4 weeks

*Controlled studies did not extend beyond 6 months.

This NDA supplement submission contains the final Clinical Study Reports (CSRs) for Pediatric Research Equity Act (PREA) PMRs No. 1356-5 and 1788-1. The sponsor proposes that these studies fulfill the commitments of the PREA Requirements in adolescents.

- PMR 1356-5: for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 to 17 years.
- PMR 1788-1: to evaluate the healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients aged 12 to 17 years.

List of 3 studies in pediatric patients aged 12 to 17 years:

ADOLESCENT CLINICAL STUDIES LISTING

Study No. No. of Centers-Country Study Start–End Dates	Study Design Primary Objective (Endpoint)	Population (a) and Type (criteria) Gender and Race (n[%]) (b) Mean Age (min-max)	Treatment Duration	Treatment (c) (Dosed/Completed)
5.3.3.2 Patient PK and Initial Tolerability Studies				
T-P107-163 3-United States 31 May 09 to 10 Sep 09	Randomized, open-label, multicenter, multiple dose, parallel-group PK, safety	36 adolescents with GERD; 18 subjects per group 14 (39%) Men, 22 (61%) Women 28 (78%) W, 8 (22%) B 14.6 (12-17) years	7 days	Capsule, 30 mg (18/18) or 60 mg (18/18)
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication				
TAK-390MR_207 8-United States, 6-Poland, 3-Portugal, 1-Mexico 22 Jun 12 to 10 Nov 14	Healing: open-label, multicenter, multiple-dose, noncomparative Maintenance: randomized, double-blind, multicenter, multiple-dose, parallel-group, placebo-controlled Efficacy (healing of EE/maintenance of healed EE), safety	Healing: 62 adolescents with EE 38 (61%) Men, 24 (39%) Women 61 (98%) W, 1 (2%) B 14.8 (12-17) years Maintenance: 51 subjects with healed EE 30 (59%) Men, 21 (41%) Women 50 (98%) W, 1 (2%) B 14.7 (12-17) years	Healing: 8 weeks Maintenance: 16 weeks Follow-up: 12 weeks	Healing: capsule, 60 mg (62/58) Maintenance: capsule, 30 mg (25/18), or placebo (26/20)
5.3.5.2 Study Reports of Uncontrolled Clinical Studies				
TAK-390MR_206 19-United States, 4-Hungary, 4-Poland, 4-Portugal, 2-Mexico, 1-Belgium, 1-Brazil, 1-Italy 22 Jun 12 to 14 Jan 14	Open-label, multicenter, multiple-dose, noncomparative Efficacy (symptomatic GERD), safety	104 adolescents with symptomatic nonerosive GERD 31 (30%) Men, 73 (70%) Women 95 (91%) W, 6 (6%) B, 3 (3%) M 15 (12-17) years	4 weeks	Capsule, 30 mg (104/102)

EE=erosive esophagitis, GERD=gastroesophageal reflux disease, PK=pharmacokinetics.
(a) Population=number of subjects who received at least 1 dose of study medication.
(b) Races: A=Asian, B=Black, M=Multiracial, O=Other, W=White.
(c) Once-daily tablets by oral administration unless otherwise noted.
(d) Median values are given.

Identified Review Issues:

No major review issue has been identified. The sponsor has not directly confirmed that the Dexilant delayed-release capsule formulation used in the 3 pediatric studies is the to-be-marketed formulation. CYP2C19 poor metabolizers were excluded from the pediatric PK study, but it is not clear whether CYP2C19 poor metabolizers were also excluded the adult PK data when comparing the PK profiles in pediatric subjects and healthy adult subjects. The sponsor did not provide the PK comparison between adolescents with gastroesophageal reflux disease (GERD) and adults with GERD. Plasma samples were analyzed for lansoprazole per the bioanalytical report for Study T-P107-163, but the sponsor did not explain why this method is appropriate for the quantification of dexlansoprazole. AUC(0-tau) was not reported for Subject 2003004, but the sponsor did not explain why this parameter was not estimable for this subject. Additionally, Subject 2003005 was excluded from the PK analysis because most of the PK samples were not collected. The reason for the missing PK samples was not provided.

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11/23/2015

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11/24/2015

4.2 Individual Study Synopsis: T-P107-163

Study T-P107-163:
A Phase 1, Randomized, Open-Label, Parallel Group, Multicenter Study to Evaluate the Pharmacokinetics and Safety of Dexlansoprazole Modified Release Capsules (30 mg and 60 mg) in Adolescents with Symptomatic Gastroesophageal Reflux Disease (GERD)

Applicant:	Takeda Global Research & Development Center, Inc.
Clinical Site:	West Coast Clinical Trials, LLC, Cypress, CA, US Advanced Clinical Research Institute, Anaheim, CA, US Vince and Associates Clinical Research, Overland Park, KS, US
Bioanalytical Site:	(b) (4)
Study Date:	05/31/2009 to 09/10/2009

Objective:

- To assess the pharmacokinetic profile and safety of dexlansoprazole delayed release capsules in pediatric patients 12 to 17 years of age with symptomatic GERD after daily administration of either 30 or 60 mg for 7 days.

Study Design:
This was a phase 1, randomized, open-label, multicenter, parallel design study of 2 dexlansoprazole delayed release capsule doses (30 and 60 mg) for 7 days. Eligible patients were randomly assigned in a ratio of 1:1 to each of the following regimen:

Regimen	Number of Subjects	Regimens
A	18	Regimen A: Dexlansoprazole capsules 30 mg administered QD for 7 days
B	18	Regimen B: Dexlansoprazole capsules 60 mg administered QD for 7 days

Reviewer's comments:
Dexlansoprazole delayed release capsules used in this study were the same formulation as the approved formulation in adults.

Study Population:
36 male and female patients, aged 12 to 17 years, with symptomatic GERD.
Patient determined to be a CYP2C19 poor metabolizer was not included in this study.

Reviewer's comments:
At the time that Study T-P107-163 was performed, PK characteristics of dexlansoprazole for the delayed-release formulation in pediatric patients were unknown. As such, a conservative approach was used by the Applicant to exclude patients who were poor metabolizers in order to reduce the risk of a pediatric patient potentially being exposed to very high plasma concentrations in this first dexlansoprazole study in the pediatric population. This approach is acceptable. The

Applicant stated (see Applicant's Response to Clinical Pharmacology Information Request, dated on 11/16/2015) that of the 61 patients who were screened for metabolizer status in Study T-P107-163, 44 patients were homozygous EMs, 16 were heterozygous EMs, and only 1 was determined to be a PM.

Excluded Medications and Dietary Products
None of the patients used concomitant medication during the study.

Pharmacokinetic Evaluation:
Blood PK samples were collected at 0 hour (predose), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, and 24 hours postdose on Day 7 to determine the plasma dexlansoprazole concentrations.

Pharmacokinetic Results:
Following daily administration of dexlansoprazole 30 or 60 mg capsules for 7 days to patients 12 to 17 years of age, plasma concentrations of dexlansoprazole displayed 2 distinct peaks, reflective of the release characteristics of the 2 granule types contained in the dexlansoprazole capsule, similar to those observed in adults.

Summary of the PK parameters of dexlansoprazole in patients 12 – 17 years of age

	Tmax (hr)	Cmax (ng/mL)	Cmax/Dose (ng/mL/mg)	AUC(0-tau) (ng·hr/mL)	AUC(0-tau)/ Dose (ng·hr/mL/mg)	T1/2(a) (hr)	CL/F (L/hr)
Regimen A: Multiple 30 mg Dose – Subjects Age 12-17 years – Day 7							
N	17	17	17	16	16	16	16
Mean	4.65	691	23.0	2886	96.21	1.66 [1.32]	12.8
SD	2.909	367.5	12.25	1355.2	45.173	0.871	6.09
Min	1.00	255	8.50	1204	40.12	0.63	5.2
Median	5.00	609	20.30	2520	83.99	1.43	11.9
Max	12.00	1600	53.33	5741	191.36	3.74	24.9
%CV	63	53	53	47	47	52	48
Regimen B: Multiple 60 mg Dose – Subjects Age 12-17 years – Day 7							
N	18	18	18	18	18	18	18
Mean	3.31	1136	18.9	5120	85.3	2.59 [2.04]	15.3
SD	1.519	582.2	9.70	2986.5	49.77	1.379	7.52
Min	1.00	399	6.65	1996	33.27	0.95	4.9
Median	3.50	1045	17.42	4124	68.73	2.36	14.57
Max	6.03	2620	43.67	12246	204.10	6.30	30.05
%CV	46	51	51	58	58	53	49

(b) Harmonic mean is shown in brackets.

Statistical analysis of dose proportionality

Parameter	Point Estimate	90% Confidence Interval
30 mg (Test) versus 60 mg (Reference) Dexlansoprazole Capsule		
Cmax/dose	1.210	0.897 – 1.630
AUC(0-tlqc)/dose	1.158	0.864 – 1.551
AUC(0-tau)/dose	1.168	0.864 – 1.579

The point estimates show that the dose normalized AUCs and Cmax for the 30 mg dexlansoprazole capsule are about 16% to 21% higher than those for the 60 mg. Overall, systematic exposure of dexlansoprazole increased approximately dose proportionally from 30 mg to 60 mg in adolescent patients, similar to that observed in adults.

Reviewer's Comments:
For study PK results and the bioanalytical method used to determine plasma dexlansoprazole concentrations, please see the Question-Based Review.

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/s/

SHEN LI
06/12/2016

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06/13/2016