Taiwan Food and Drug Administration

Assessment Report

Trade Name：恩疼停 注射劑 / EMGALITY injection

Active Ingredient：Galcanezumab

License Number：MOHW-BI 001113

Applicant：台灣禮來股份有限公司

Approval Date：2019/10/04

Indication：

適用於預防成人偏頭痛。

EMGALITY is indicated for the preventive treatment of migraine in adults.

1. Background Information

Trade Name	恩疼停 注射劑 / EMGALITY injection
Active Ingredient(s)	Galcanezumab
Applicant	台灣禮來股份有限公司
Dosage Form & Strengths	Solution for Injection 120mg
Indication	適用於預防成人偏頭痛。 EMGALITY is indicated for the preventive treatment of migraine in adults.
Posology	EMGALITY 的建議劑量為一次注射 240 mg（連續兩次皮下注射，每次 120 mg）做為負荷劑量 (loading dose)，之後每月皮下注射 120 mg 的劑量。 如果漏掉一劑 EMGALITY，應儘快給藥。此後，可以自接受最後一劑之日起安排每月一次 EMGALITY 的用藥。 The recommended dosage of EMGALITY is 240 mg (two consecutive subcutaneous injections of 120 mg each) once as a loading dose, followed by monthly doses of 120 mg injected subcutaneously. If a dose of EMGALITY is missed, administer as soon as possible. Thereafter, EMGALITY can be scheduled monthly from the date of the last dose.
Pharmacological Category **ATC Code**	N02CX08

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance of EMGALITY is galcanezumab. Galcanezumab is a humanized IgG4 monoclonal antibody designed to bind calcitonin gene-related peptide (CGRP), inhibiting its activity as a sensory neuropeptide in the trigeminal system – a fundamental mechanism in the pathophysiology of migraine.

Each heavy chain of galcanezumab contains a single N-linked glycosylation site at Asn296. The molecular weight of galcanezumab is 144.1 kDa for non-glycosylated form. Galcanezumab is produced in Chinese Hamster Ovary (CHO) production cell line by recombinant DNA technology. It is manufactured at ImClone Systems LLC, Branchburg, USA.

The source, history and generation of the cell substrate, control of cell banking system, quality control of raw material, process validation with proper in-process controls, validation of viral clearance, specification, and batch analysis were provided to demonstrate the safety, quality and consistency. Comparability studies were performed to support changes introduced during development to the commercial stage. Structure elucidation and characterization studies for galcanezumab were performed using extensive physicochemical, biophysical and biological methods. The product-related and process-related impurities in galcanezumab were also well characterized and controlled. The proposed shelf-life of galcanezumab drug substance is 24 months at 2-8°C storage condition.

2.1.2 Drug Product

The drug product (EMGALITY injection) is supplied as a 120-mg/mL solution and is a clear to opalescent, colorless to slightly yellow to slightly brown, free of visible particles, sterile, and non-pyrogenic parenteral solution for subcutaneous administration. Each mL is composed of galcanezumab (120 mg); L-histidine (0.5 mg); L-histidine hydrochloride monohydrate (1.5 mg); Polysorbate 80 (0.5 mg); Sodium Chloride (8.8 mg); Water for Injection. The pH range is 5.3-6.3. All excipients comply with the pharmacopoeia (USP, EP, or JP). No novel excipients or animal/human origins are used in the formulation.

Galcanezumab drug product is contained in a 1-mL-long, Type I borosilicate glass syringe barrel with laminated bromobutyl elastomeric plunger. The container closure system filled with drug product is referred to as the semi-finished syringe (SFS). The SFS is assembled into a delivery device (Autoinjector) for patient administration.

The drug product is manufactured at Eli Lilly and Company, Indianapolis, USA. The release and shelf-life specifications include appearance, identity, purity, impurity, potency, sterility, endotoxin, and other general quality tests. Analytical methods and related validations were provided. Process validation and batch analysis were provided to demonstrate the quality and consistency of drug product. The proposed shelf-life is 24 months at the recommended storage condition (2-8°C).

In conclusion, the CMC document provided is appropriate to support the quality and consistency of EMGALITY.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The active ingredient of EMGALITY is galcanezumab. Galcanezumab bound to human (monkey) and rat (mouse) CGRP with a K_D at sub-nanomolar level, and had an approximate 8-fold higher affinity to human (monkey) CGRP compared to rat (mouse) CGRP. Galcanezumab blocked both human and rabbit CGRP-induced cAMP generation in a cell line expressing the human CGRP receptor. Galcanezumab could also inhibit the activation of

AMY1 receptors by CGRP. On the other hand, galcanezumab did not bind to human CGRP receptor, AMY1 receptor or the other members of the calcitonin family of peptides including amylin, calcitonin, adrenomedullin, and intermedin. Galcanezumab did not bind to any of the Fcγ receptors tested (CD16a, CD32a, and CD64) nor to the complement component C1q.

In vivo pharmacology studies showed that galcanezumab prevents capsaicin-induced dermal blood flow increase in rats and monkeys. Safety pharmacology of galcanezumab was evaluated in the repeat-dose toxicity studies in monkeys; no galcanezumab-related adverse findings were noted up to the highest dose examined.

2.2.2 Toxicological Studies

In general toxicity studies, no significant toxicities were observed in galcanezumab-treated rats or monkeys. Non-adverse injection site reactions were noted in both animal species. Gender differences in the toxicokinetic data were noted in rats. No adverse galcanezumab-related changes in fertility, embryo-fetal development, pre- and post-natal development or juvenile animals were identified. A carcinogenicity assessment of galcanezumab indicated that the carcinogenic potential of galcanezumab is low.

The incidence of (suspected) anti-drug antibodies was low-to-moderate in rats and low in monkeys and rabbits. Ex vivo tissue cross-reactivity studies were not completed due to the method was not optimized. The specifications of impurities were supported by the 6-month repeat-dose toxicology study in monkeys.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The pharmacokinetics of galcanezumab was approximately dose-proportional in healthy subject following subcutaneous administration over a dose range of 1 to 600 mg. A loading dose of 240 mg achieved the serum galcanezumab steady-state concentration after the first dose. The time to maximum concentration is 5 days, and the elimination half-life is 27 days. Site of administration (abdomen, thigh, back of the upper arm, and buttocks) was not found to be a significant covariate for galacanezumab exposure based on population PK analysis.

There was no difference in pharmacokinetic parameters between healthy volunteers and patients with episodic or chronic migraine. The apparent volume of distribution (V/F) of galcanezumab was 7.3 L. Galcanezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. The apparent clearance (CL/F) of galcanezumab-gnlm was 0.008 L/h.

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been conducted. Galcanezumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant

medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

2.3.3 Special Populations

Age (18 to 65 years old), gender, renal impairment (CL_{cr} 24 to 308 ml/min), and hepatic impairment had no significant effect on the pharmacokinetics of based on population pharmacokinetics analysis. No pharmacokinetic data are available for pediatric patients, geriatric patient and severe renal impairment patient.

Presence of ADA, irrespective of titer and neutralizing Ab, did not seem to affect the PK, of galcanezumab in patients. However, this was based on limited data from patients who were ADA positive and only one open label phase 3 study had one year data. The available data are limited to make definite conclusions.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, the Sponsor provided three phase III studies ([I5Q-MC-CGAG], [I5Q-MC-CGAH] and [I5Q-MC-CGAI]) to support the efficacy of galcanezumab injection for the claimed indication. The major design features of three studies were summarized as follows:

- ***Studies [I5Q-MC-CGAG] and [I5Q-MC-CGAH] (Episodic Migraine):***

The pivotal studies CGAG and CGAH had similar design. Both were Phase 3, multicenter, randomized, double-blind, placebo-controlled study of galcanezumab in patients suffering from episodic migraine. The primary endpoint was the overall mean change from baseline in the number of monthly Migraine Headache Days (MHDs) during the 6-month double-blind treatment phase. After multiplicity adjustment, both galcanezumab 120 mg and 240 mg treatment groups were statistically significantly superior to placebo in the prevention of migraine as demonstrated by an overall mean reduction in monthly MHDs across the double-blind period (Table 1). Galcanezumab treatment with the 240 mg once-monthly dose did not show additional benefit over the Galcanezumab 120 mg once-monthly dose.

In both episodic migraine Studies CGAG and CGAH, both doses of galcanezumab were statistically significantly superior to placebo on all key secondary endpoints after adjustment for multiplicity (Table 2 and Table 3).

- ***Study [I5Q-MC-CGAI] (Chronic Migraine):***

Study CGAI was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of galcanezumab in patients suffering from chronic migraine. The primary endpoint was the overall mean change from baseline in the number of monthly MHDs during the 3-month

double-blind treatment phase. After multiplicity adjustment, both galcanezumab 120 mg and 240 mg treatment groups were statistically significantly superior to placebo in the prevention of migraine as demonstrated by an overall mean reduction in monthly MHDs across the double-blind period (Table 1). Galcanezumab treatment with the 240 mg once-monthly dose did not show additional benefit over the Galcanezumab 120 mg once-monthly dose.

After multiplicity adjustment, the 240 mg was superior to placebo on all key secondary objectives except for 100% response rate; and the 120 mg dose was superior to placebo only on the key secondary outcome of ≥50% response (Table 2 and Table 3).

Table 1 Primary Efficacy Analysis: Overall Mean Change in Monthly Migraine Headache Days (Studies CGAG, CGAH, and CGAI, ITT)

Results	Change from Baseline in Number of Monthly Migraine Headache Days								
	CGAG (Months 1 to 6)			CGAH (Months 1 to 6)			CGAI (Months 1 to 3)		
	PBO N=425	GMB 120 mg N=210	GMB 240 mg N=208	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
LSMean Change	**-2.81**	**-4.73**	**-4.57**	**-2.28**	**-4.29**	**-4.18**	**-2.74**	**-4.83**	**-4.62**
(SE)	(0.24)	(0.29)	(0.29)	(0.20)	(0.25)	(0.26)	(0.36)	(0.44)	(0.43)
Difference vs		-1.92	-1.76		-2.02	-1.90		-2.09	-1.88
Placebo (SE)		(0.28)	(0.28)		(0.27)	(0.27)		(0.42)	(0.42)
95% CI on		(-2.48,	(-2.31,		(-2.55,	(-2.44,		(-2.92,	(-2.71,
Difference		-1.37)	-1.20)		-1.48)	-1.36)		-1.26)	-1.05)
P-value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Adjusted significance threshold (α)[a]		0.026	0.026		0.026	0.026		0.026	0.026
Result (S or NS)		S	S		S	S		S	S

Abbreviations: CI = confidence interval, not adjusted for multiplicity; GMB = galcanezumab; LSMean = Least Squares Mean; N = total number of patients; NS = not significant after adjustment for multiplicity; PBO = placebo; S = significant after adjustment for multiplicity; SE = standard error.

a Note: if p-value is less than or equal to the adjusted significance threshold, then the results are statistically significant.

Table 2 Results of key secondary efficacy analyses (Studies CGAG, CGAH, and CGAI, ITT)

Results	CGAG (Months 1 to 6)			CGAH (Months 1 to 6)			CGAI (Months 1 to 3)		
	PBO N=425	GMB 120 mg N=210	GMB 240 mg N=208	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
≥50% MHDs Responders [a]									
Percentage, %	**38.6**	**62.3**	**60.9**	**36.0**	**59.3**	**56.5**	**15.4**	**27.6**	**27.5**
(SE)	(1.7)	(2.4)	(2.5)	(1.7)	(2.4)	(2.5)	(1.6)	(2.7)	(2.6)
Odds Ratio vs Placebo		2.63	2.48		2.60	2.31		2.09	2.08
95% CI on Odds Ratio		2.05, 3.37	1.94, 3.18		2.03, 3.32	1.81, 2.96		1.56,2.8	1.55, 2.78
P-value vs placebo		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Adj. Sig. Threshold (α)[b]		0.025	0.025		0.025	0.025		0.0125	0.025
Result (S or NS)		S	S		S	S		S	S
≥75% MHDs Responders[a]									
Percentage, %	**19.3**	**38.8**	**38.5**	**17.8**	**33.5**	**34.3**	**4.5**	**7.0**	**8.8**
(SE)	(1.4)	(2.4)	(2.4)	(1.3)	(2.3)	(2.3)	(0.9)	(1.4)	(1.7)
Odds Ratio vs Placebo		2.65	2.62		2.34	2.42		1.60	2.04
95% CI on Odds Ratio		2.04, 3.45	2.01, 3.41		1.78, 3.06	1.84, 3.17		1.04, 2.46	1.36, 3.06
P-value vs placebo		<0.001	<0.001		<0.001	<0.001		0.031	<0.001
Adj. Sig. Threshold (α)[b]		0.025	0.025		0.025	0.025		0.025	0.025
Result (S or NS)		S	S		S	S		NS[C]	S
100% MHDs Responders[a]									
Percentage, %	**6.2**	**15.6**	**14.6**	**5.7**	**11.5**	**13.8**	**0.5**	**0.7**	**1.3**
(SE)	(0.8)	(1.6)	(1.6)	(0.7)	(1.4)	(1.5)	(0.3)	(0.4)	(0.6)
Odds Ratio vs Placebo		2.80	2.61		2.16	2.67		1.37	2.61
95% CI on Odds Ratio		1.96, 4.01	1.81, 3.75		1.50, 3.12	1.87, 3.81		0.43, 4.37	0.97, 7.04
P-value vs placebo		<0.001	<0.001		<0.001	<0.001		0.597	0.058
Adj. Sig. Threshold (α)[b]		0.025	0.025		0.025	0.025		0	0.025
Result (S or NS)		S	S		S	S		Not tested[c]	NS

Abbreviations: Adj. = adjusted; CI = Confidence interval; GLIMMIX = generalized linear mixed model (for binary variables); GMB = galcanezumab; LSMean = least square means estimated from MMRM; MHD = migraine headache day; MMRM = mixed-model repeated measures; MSQ = Migraine-Specific Quality of Life Questionnaire Version 2.1; NS = not significant after adjustment for multiplicity; PBO = placebo; PGI-S = Patient Global Impression of Severity; S = significant after adjustment for multiplicity; SE = standard error; Sig. = significance

a Results for continuous variables are from MMRM; results for response rates are from GLIMMIX. Results presented for PGI-S and MSQ Role Function-Restrictive for Studies CGAG and CGAH are for the average of Months 4 to 6 and for Study CGAI are at Month 3; results for presented all other measures are the overall result at the end of the study (average of all months).

b If p-value is less than or equal to the adjusted significance level, then the results are statistically significant after adjustment for multiplicity.

c Because of the nonsignificant result observed for the 75% response rate for the 120 mg dose in Study CGAI and because no alpha can be recycled from galcanezumab 240 mg to 120 mg since the result for galcanezumab 240 mg 100% response rate was nonsignificant (refer to the multiple testing procedure described in ISE Section 5.4.5), all remaining items in the testing sequence (MHD with acute medication use, MSQ-Role Function-Restrictive, PGI-S, and 100% response rate) for the 120 mg dose for Study CGAI are considered not statistically significant regardless of p-value.

Table 3 Results of key secondary efficacy analyses (Studies CGAG, CGAH, and CGAI, ITT)

Results	CGAG (Months 1 to 6)			CGAH (Months 1 to 6)			CGAI (Months 1 to 3)		
	PBO	**GMB 120 mg**	**GMB 240 mg**	**PBO**	**GMB 120 mg**	**GMB 240 mg**	**PBO**	**GMB 120 mg**	**GMB 240 mg**
Change from Baseline in Number of MHDs per Month with Acute Medication Use[a]									
N	425	210	208	450	226	220	538	273	274
LSMean Change	**-2.15**	**-3.96**	**-3.76**	**-1.85**	**-3.67**	**-3.63**	**-2.23**	**-4.74**	**-4.25**
(SE)	(0.21)	(0.25)	(0.26)	(0.18)	(0.22)	(0.23)	(0.33)	(0.40)	(0.40)
Diff. vs Placebo		-1.81	-1.61		-1.82	-1.78		-2.51	-2.01
(SE)		(0.24)	(0.24)		(0.24)	(0.24)		(0.38)	(0.38)
95% CI on Difference		-2.28,-1.33	-2.09,-1.14		-2.29, -1.36	-2.25,-1.31		-3.27,-1.76	-2.77,-1.26
P-value vs placebo		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Adj. Sig. Threshold (α)[b]		0.0125	0.0125		0.0125	0.0125		0	0.0125
Result (S or NS)		S	S		S	S		Not tested[c]	S
	CGAG (Months 4 to 6)			**CGAH (Months 4 to 6)**			**CGAI (Month 3)**		
Change from Baseline in MSQ Role Function-Restrictive[a]									
N	377	189	184	396	213	210	494	252	253
LSMean Change	**24.69**	**32.43**	**32.09**	**19.65**	**28.47**	**27.04**	**16.76**	**21.81**	**23.05**
(SE)	(1.07)	(1.31)	(1.32)	(0.92)	(1.15)	(1.17)	(1.18)	(1.41)	(1.63)
Diff. vs Placebo		7.74	7.40		8.82	7.39		5.06	6.29
(SE)		(1.29)	(1.31)		(1.27)	(1.28)		(1.50)	(1.66)
95% CI on Difference		5.20, 10.28	4.83, 9.97		6.33, 11.31	4.88, 9.90		2.12,7.99	3.03, 9.55
P-value vs placebo		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Adj. Sig. Threshold (α)[b]		0.025	0.025		0.025	0.025		0	0.025
Result (S or NS)		S	S		S	S		Not tested[c]	S
Change from Baseline in PGI-S[a]									
N	377	189	184	396	213	210	494	252	253
LSMean Change	**-1.27**	**-1.59**	**-1.55**	**-0.94**	**-1.22**	**-1.17**	**-0.62**	**-0.76**	**-0.91**
(SE)	(0.08)	(0.10)	(0.10)	(0.07)	(0.08)	(0.08)	(0.08)	(0.10)	(0.10)
Diff. vs Placebo		-0.32	-0.28		-0.29	-0.23		-0.14	-0.28
(SE)		(0.10)	(0.10)		(0.09)	(0.09)		(0.10)	(0.10)
95% CI on Difference		-0.52, -0.12	-0.48,-0.07		-0.47, -0.11	-0.41, -0.05		-0.34,0.06	-0.48,-0.08
P-value vs placebo		0.002	0.008		0.002	0.012		0.181	0.006
Adj. Sig. Threshold (α)[b]		0.025	0.025		0.025	0.025		0	0.025
Result (S or NS)		S	S		S	S		Not tested[c]	S

Abbreviations: Adj. = adjusted; CI = Confidence interval; GLIMMIX = generalized linear mixed model (for binary variables); GMB = galcanezumab; LSMean = least square means estimated from MMRM; MHD = migraine headache day; MMRM = mixed-model repeated measures; MSQ = Migraine-Specific Quality of Life Questionnaire Version 2.1; NS = not significant after adjustment for multiplicity; PBO = placebo; PGI-S = Patient Global Impression of Severity; S = significant after adjustment for multiplicity; SE = standard error; Sig. = significance

a Results for continuous variables are from MMRM; results for response rates are from GLIMMIX. Results presented for PGI-S and MSQ Role Function-Restrictive for Studies CGAG and CGAH are for the average of Months 4 to 6 and for Study CGAI are at Month 3; results for presented all other measures are the overall result at the end of the study.
b If p-value is less than or equal to the adjusted significance level, then the results are statistically significant after adjustment for multiplicity.
c Because of the nonsignificant result observed for the 75% response rate for the 120 mg dose in Study CGAI and because no alpha can be recycled from galcanezumab 240 mg to 120 mg since the result for galcanezumab 240 mg 100% response rate was nonsignificant, all remaining items in the testing sequence for the 120 mg dose for Study CGAI are considered not statistically significant regardless of p-value

2.4.2 Safety Results

Major TEAEs include injection site reactions/erythema, hypersensitivity, vertigo and constipation. Patients with CV events within 6 months, previous stroke, and EKG showing CV risks were excluded from pivotal studies; hence the safety is not explored in this population.

2.5 Bridging Study Evaluation

PK/PD perspective

After single dosing 120 mg in healthy Japanese, the C_{max} and AUC_{inf} of galcanezumab were 1.2-fold and 1.18-fold increase compared to healthy Caucasian. At the recommended dose regimen (240 mg loading dose following 120 mg Q4W), the $C_{max,ss}$ and $AUC_{tau,ss}$ of galcanezumab in East-Asian target population were 1.26-fold and 1.27-fold increase compared to non-East-Asian target population.

Considering (1) the inter-subject variation of galcanezumab was about 50% via SC route at single dose of 1 to 600 mg and (2) the metabolism pathway of galcanezumab is via catabolism seldom affected by genetic polymorphism, therefore galcanezumab was considered none to minimally ethnically sensitive between Asian and non-Asian from PK aspect.

Clinical perspective

Summary report of Japanese study CGAN was provided, the study design is the same as CGAG and CGAH. The efficacy results are consistent with global trials as shown in the following table. Safety profile of Study CGAN is similar to that of global trials.

	Placebo N=230	LY 120 mg N=115	LY 240 mg N=114
Baseline (Mean [SD])	8.63 (2.95)	8.60 (2.80)	8.99 (2.99)
LS mean change from baseline (SE)	-0.59 (0.23)	-3.60 (0.33)	-3.36 (0.33)
Difference vs. placebo (95% CI)		-3.01(-3.80, -2.22)	-2.77 (-3.56, -1.98)
p-value (multiplicity adjusted)		<0.001	<0.001

In summary, the efficacy results and safety profiles in Asian population were comparable to

those observed in overall population.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. Three adequate and well-controlled clinical studies were provided to demonstrate the efficacy of galcanezumab for the preventive treatment of migraine in adults. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure that the benefits of the drug outweigh the risks. In conclusion, the overall benefit/risk ratio is favorable to support regular approval of the claimed indications.

3. Post-Marketing Requirements

(1) Submit the complete study report of Japanese study I5Q-JE-CGAN once available.
(2) Routine pharmacovigilance should be conducted.