Taiwan Food and Drug Administration

Assessment Report

Trade Name：安莫疼注射液劑 70 毫克/毫升 /
AIMOVIG 70mg/mL solution for injection
安莫疼注射液劑 140 毫克/毫升 /
AIMOVIG 140mg/mL solution for injection

Active Ingredient：Erenumab

License Number：MOHW-BI 001127

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Applicant：台灣諾華股份有限公司

Approval Date：2020/04/24

Indication：

預防成人偏頭痛。

AIMOVIG is indicated for the prophylaxis of migraine in adults.

1. Background Information

Trade Name	安莫疼注射液劑 70 毫克/毫升 / AIMOVIG 70 mg/mL solution for injection 安莫疼注射液劑 140 毫克/毫升 / AIMOVIG 140 mg/mL solution for injection
Active Ingredient(s)	Erenumab
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	Solution for Injection 70 mg/mL, 140 mg/mL
Indication	預防成人偏頭痛。 AIMOVIG is indicated for the prophylaxis of migraine in adults.
Posology	建議劑量為 70 mg，每月一次。某些病人可能受益於每月給予一次 140 mg 的劑量。 The recommended dosage of AIMOVIG is 70 mg injected subcutaneously once monthly. Some patients may benefit from a dosage of 140 mg injected subcutaneously once monthly.
Pharmacological Category **ATC Code**	N02CX07

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

The 70 mg/mL and 140 mg/mL drug product are supplied as a sterile, single-use, preservative-free solution for subcutaneous (SC) injection in a prefilled syringe (PFS) with and without Autoinjector/Pen (AI/Pen).

2.1.1 Drug substance

Manufacturing

- Amgen Singapore Manufacturing Pte. Ltd. (referred to as ASM) is the proposed commercial manufacturing site for the drug substance.
- The process included cell culture process, purification process and the final filtration and storage process, which has been described in sufficient detail with the accompanied process flow diagrams.

Controls

- The source and history of the host cell line were provided.
- The construction of expression vector and generation of the cell substrate have been described.
- Product quality in-process controls, process consistency in-process controls and critical

process parameters were provided.

- Adventitious agents
  - No raw materials of human or animal origins are used in the DS manufacturing process and TSE/BSE risk is negligible.
  - Bacteria and fungi, mycoplasma as well as virus tests are performed on each unprocessed bulk.
  - The results of the virus clearance studies, retroviral like particles observed in unprocessed bulk by TEM, and the estimated safety margin retroviral contamination per clinical dose is considered acceptable.
  - Overall, the risk assessment of adventitious agents associated with AMG334 drug substance is considered adequate.

Process validation

The validation of the AMG334 drug substance commercial manufacturing process was carried out on 3 lots. The results demonstrated the process is repeatable.

Manufacturing process development

The process development history was provided and the process changes were implemented. Based on the comparability bridging studies, it is confirmed that DS manufactured by the commercial process has a highly comparable quality profile with those made by previous developmental manufacturing processes.

Characterization

AMG334 product was characterized using biochemical, biophysical, biological, and forced degradation studies.

DS specification

The specifications and test methods used to assure the quality of the drug substance at release were provided. The release testing of AMG334 drug substance includes appearance, color, pH, identity, purity, content, potency and quantity.

Reference materials

A two-tiered reference standards consisting of a primary reference standards and a working reference standards have been established for lot release and stability testing for DS and DP. The qualification reports of current RSs have been provided.

Stability

The 24 months shelf-life for DS at storage condition of -30℃ is suggested on the basis of results of comparability study and real-time/real-temperature stability study for DS from ATO by process 2 (commercial).

2.1.2 Drug product PFS and AI/Pen

70 mg/mL AIMOVIG PFS and AI/Pen: The PFS and AI/Pen contains a 1.0 mL deliverable volume of 70 mg/mL AMG 334 (erenumab) in formulation buffer (acetate, sucrose,

polysorbate 80, pH 5.2).

140 mg/mL AIMOVIG PFS and AI/Pen: The PFS and AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL AMG 334 (erenumab) in formulation buffer (acetate, sucrose, polysorbate 80, pH 5.2).

Drug product manufacturing

AMG334 drug product is manufactured at Amgen Manufacturing Ltd (AML).

Assembly of pre-filled syringe in the auto-injector and secondary packaging occurs at Amgen Europe B.V. (ABR) and Amgen Technology (Ireland Unlimited) company.

The AMG334 PFS and AI/Pen drug product manufacturing process consists of the following unit operations: formulation buffer preparation, drug substance thaw, drug product formulation, bioburden reduction filtration, filtered formulated drug product hold, sterile filtration, and aseptic filling, syringe plunger-stopper placement, inspection, and storage. The additional process for AI/Pen is to assemble the pre-filled syringe into the auto-injector.

Drug product manufacturing process controls

The critical process parameters, in-process control tests that control the critical steps have been provided.

Drug product process validation

The AMG 334 drug product manufacturing activities at AML included the following processing steps: drug substance thaw, formulation buffer preparation, drug product formulation and bioburden reduction filtration, filtered formulated drug product hold and sterile filtration, aseptic filling and plunger-stopper placement of the filled syringes.

Overall, the validation studies have demonstrated that the manufacturing process of AMG 334 drug product at AML is robust.

Drug product manufacturing process development

The history of drug product process development was provided. Based on the comparability bridging studies, it supported that drug product manufactured by the commercial process has a highly comparable quality profile with those made by previous developmental manufacturing processes.

Drug product specification

For AMG334 70 mg/ 1 ml solution and AMG334 140 mg/ 1 ml solution in PFS with and without AI/Pen drug product, the specifications include general test (appearance, color, clarity pH, osmolality, and sub-visible particles), quantity (protein concentration and deliverable volume), identity, purity/impurities (size and charge variants), potency, endotoxins, and sterility. In addition, the device functionality tests for AI/Pen include injection time and deliverable volume.

Stability of the Drug product

The stability studies were provided. The 24 months shelf life for AIMOVIG 70 mg/ml PFS and AI/Pen, and the 18 months shelf life for AIMOVIG 140 mg/ml PFS and AI/Pen are suggested on the basis of real-time/real-temperature results.

2.2 Preclinical Pharmacology/Toxicology Evaluation

The active ingredient is erenumab. Erenumab is directed against the calcitonin gene-related peptide (CGRP) receptor which is located at sites that are relevant to migraine pathophysiology.

2.2.1 Pharmacological Studies

Erenumab bound with 10,000-fold higher affinity at the human CGRP receptor complex compared to rabbit or dog CGRP receptors. Erenumab potently antagonized human and monkey CGRP receptors but did not block the rat receptor. On the other hand, erenumab showed low or few effects on CGRP receptor of rat, rabbit or dog. Erenumab did not either agonize or antagonize with the family of structurally related receptors, including AM1, AM2, calcitonin, and amylin receptors. Moreover, erenumab inhibited the capsaicin-induced increase in dermal blood flow in a dose-dependent manner in vivo. A safety pharmacology study in monkeys showed that no erenumab-related adverse events were observed in respiratory, cardiovascular or central nervous system in the high dose group.

2.2.2 Toxicological Studies

In 1- and 6-month repeat-dose toxicity studies in monkeys, minimal to mild cell infiltration was observed at injection sites. Anti-drug antibodies (ADAs) were detected in some erenumab-treated animals. Circulating immune complex (CIC) and its related pathology was noted in 1 animal each of the 2 studies, and 1 animal was euthanized. Considering that CIC may occur in experimental animals receiving human proteins and no ADA-related sequelae has been noted in previous trials, formation of CIC may not be a direct effect of erenumab.

In the enhanced pre-/postnatal developmental toxicity study in monkeys, no erenumab -related changes were observed. According to ICH S6 (R1) guidance, it is acceptable that no genotoxicity studies were conducted with erenumab. An assessment was provided to support the low carcinogenic risk of erenumab. Results of tissue cross-reactivity assays in addition to that of general toxicity studies revealed no potential safety concern of erenumab. Erenumab did not induce any contraction of the proximal or distal coronary artery segments in an ex vivo assay.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Erenumab exhibits non-linear kinetics as a result of binding to the CGRP receptor. Erenumab exposure increases more than the dose proportional from 1 to 70 mg and approximately dose proportionally from 70 to 210 mg following a single subcutaneous administration.

Less than 2-fold accumulation was observed in trough serum concentrations (C_{min}) for episodic and chronic migraine patients following subcutaneous administration of 70 mg once monthly and 140 mg once monthly doses. Serum trough concentrations approached steady state by 3 months of dosing. The effective half-life of erenumab is 28 days.

Following a single subcutaneous dose of 140 mg or 70 mg erenumab administered to healthy adults, median peak serum concentrations were attained in 4 to 6 days, and estimated absolute bioavailability was 82%. Following a single 140 mg intravenous dose, the mean (SD) volume of distribution during the terminal phase (V_z) was estimated to be 3.86 (0.77) L.

Two elimination phases were observed for erenumab. At low concentrations, the elimination is predominately through saturable binding to target (CGRP-R), while at higher concentrations the elimination of erenumab is largely through a non-specific proteolytic pathway.

2.3.2 Interaction Studies

Erenumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

In an open-label drug interaction study in healthy female volunteers, erenumab (140 mg subcutaneous, single-dose) did not affect the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and norgestimate. In a study in healthy volunteers, concomitant administration of erenumab with sumatriptan had no effect on the pharmacokinetics of sumatriptan.

2.3.3 Special Populations

Age (18 to 65 years old), gender, and renal impairment had no significant effect on the pharmacokinetics of erenumab based on population pharmacokinetics analysis. No pharmacokinetic data are available for pediatric patients, geriatric patient and severe renal impairment patient.

No studies have been performed in patients with hepatic impairment. Erenumab, as a human monoclonal antibody, is not metabolized by cytochrome P450 enzymes and hepatic clearance is not a major clearance pathway for erenumab.

Mean trough levels of erenumab (week 12) among subjects developing anti-erenumab binding antibodies were 40% and 35% lower than antibody-negative subjects receiving 140 mg or 70 mg dose, respectively. Considering the inter-subject variation of erenumab, the

effect of ADA status might not be clinical meaningful.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One phase II study in chronic migraine (Study 20120295) and two phase III studies in episodic migraine (Studies 20120296 and 20120297) were reviewed to evaluate the efficacy and safety of erenumab in the prophylaxis of migraine in adults. Episodic migraine is defined as <15 migraine days per month. Chronic migraine is defined as 15 or more headache days per month, at least 8 of which have to be typical migraine days.

Study 20120295 (chronic migraine)

The primary endpoint for Study 20120295 was the change in monthly migraine days (MMD) from baseline to the last 4 weeks of the 12-week double-blind treatment phase (DBTP). Secondary efficacy endpoints included the achievement of at least a 50% reduction from baseline in MMD in the last 4 weeks of the 12-week DBTP; change from baseline in monthly acute migraine-specific medication treatment days in the last 4 weeks of the 12-week DBTP; and change from baseline in cumulative monthly headache hours in the last 4 weeks of the 12-week DBTP. A sequential testing procedure, specifically, the hierarchical gate-keeping procedures and Hochberg method, was used to maintain the 2-sided study-wise type I error at 0.05 between the 2 erenumab doses and the primary and secondary endpoints.

Between March 2014 and April 2016, 667 subjects were randomized in a 3:2:2 ratio to receive placebo (286 subjects), erenumab 70 mg (191 subjects), or erenumab 140 mg (190 subjects) monthly (QM [every 4 weeks]) by subcutaneous (SC) injection for the duration of the 12-week DBTP. A total of 656 subjects were included in the Efficacy Analysis Set.

There was a statistically significant greater mean reduction in the change in MMD from baseline to the last 4 weeks of the 12-week DBTP for erenumab 70 mg and erenumab 140 mg compared with placebo. The least squares mean (LSM) difference (95% CI) was -2.46 (-3.52, -1.39) days for erenumab 70 mg vs placebo and -2.45 (-3.52, -1.38) days for erenumab 140 mg vs placebo (both $p < 0.001$).

The proportion of subjects with at least a 50% reduction in MMD from baseline to the last 4 weeks of the 12-week DBTP was 23.5%, 39.9%, and 41.2% for the placebo, erenumab 70-mg, and erenumab 140-mg groups, respectively. The odds ratios (95% CI) were 2.18 (1.46, 3.27) for erenumab 70 mg vs placebo and 2.34 (1.56, 3.51) for erenumab 140 mg vs placebo; results were statistically significant for each erenumab group vs placebo (both $p < 0.001$).

The LSM difference (95% CI) in the change from baseline in monthly acute migraine-specific medication treatment days during the last 4 weeks of the 12-week DBTP was -1.86 (-2.60, -1.13) days for erenumab 70 mg vs placebo and -2.55 (-3.28, -1.82) days

for erenumab 140 mg vs placebo. The results were both statistically significant (both $p < 0.001$).

There was no statistically significant mean difference in the change in cumulative monthly headache hours from baseline to the last 4 weeks of the 12-week DBTP for erenumab 70 mg and erenumab 140 mg compared with placebo. The LSM difference (95% CI) in the change in cumulative monthly headache hours was -9.54 (-26.98, 7.90) hours for erenumab 70 mg vs placebo ($p = 0.28$) and -19.31 (-36.71, -1.92) hours for erenumab 140 mg vs placebo ($p = 0.030$).

Study 20120296 (episodic migraine)

The primary endpoint for Study 20120296 was the change in mean MMD from baseline to the last 3 months (months 4, 5, and 6) of the 24-week DBTP. Secondary efficacy endpoints included the achievement of at least a 50% reduction from baseline in mean MMD over the last 3 months of the 24-week DBTP; change from baseline in mean monthly acute migraine-specific medication treatment days over the last 3 months of the 24-week DBTP; change from baseline in mean monthly average physical impairment domain scores over the last 3 months of the DBTP as measured by the MPFID; and change from baseline in mean monthly average impact on everyday activities domain scores over the last 3 months of the DBTP as measured by the MPFID. A sequential testing procedure, specifically, the hierarchical gate-keeping procedures and Hochberg method, was used to maintain the 2-sided study-wise type I error at 0.05 between the 2 erenumab doses and the primary and secondary endpoints.

Between July 2015 and September 2016, 955 subjects were randomized in a 1:1:1 ratio to receive placebo (319 subjects), erenumab 70 mg (317 subjects), or erenumab 140 mg (319 subjects) monthly by subcutaneous injection for the duration of the 24-week DBTP. A total of 946 subjects were included in the Efficacy Analysis Set.

There was a statistically significant greater mean reduction in the change in mean MMD from baseline to the last 3 months of the 24-week DBTP for erenumab 70 mg and erenumab 140 mg as compared with placebo. The LSM difference (95% CI) was -1.40 (-1.88, -0.92) days for erenumab 70 mg vs placebo and -1.85 (-2.33, -1.37) days for erenumab 140 mg versus placebo (both $p < 0.001$).

The proportion of subjects with at least a 50% reduction in MMD from baseline to the last 3 months of the 24-week DBTP was 26.6%, 43.3%, and 50.0% for the placebo, erenumab 70-mg, and erenumab 140-mg groups, respectively. The odds ratios (95% CI) were 2.13 (1.52, 2.98) for erenumab 70 mg vs placebo and 2.81 (2.01, 3.94) for erenumab 140 mg vs placebo; results were statistically significant for each erenumab group vs placebo (both $p < 0.001$).

There was a statistically significant greater mean reduction in mean monthly acute migraine-specific medication treatment days from baseline to the last 3 months of the 24-week DBTP for erenumab 70 mg and erenumab 140 mg compared with placebo. The LSM difference (95% CI) was -0.94 (-1.23, -0.64) days for erenumab 70 mg vs placebo and -1.42 (-1.71, -1.12) days for erenumab 140 mg vs placebo (both $p < 0.001$).

There was a statistically significant greater mean reduction in mean monthly average MPFID physical impairment domain score from baseline to the last 3 months of the DBTP for erenumab 140 mg and erenumab 70 mg compared to placebo. The LSM difference (95% CI) was -2.43 (-3.51, -1.35) for erenumab 140 mg vs placebo and -1.86 (-2.95, -0.77) for erenumab 70 mg vs placebo (both $p < 0.001$).

There was a greater mean reduction in mean monthly average MPFID everyday activities domain scores from baseline to the last 3 months of the DBTP for erenumab 140 mg and erenumab 70 mg compared to placebo. The LSM difference (95% CI) was -2.57 (-3.62, -1.51) for erenumab 140 mg vs placebo and -2.22 (-3.28, -1.16) for erenumab 70 mg vs placebo (both $p < 0.001$).

Study 20120297 (episodic migraine)

The primary endpoint for Study 20120297 was the change from baseline in MMD from baseline in the last 4 weeks of the DBTP. Secondary efficacy endpoints included the achievement of at least a 50% reduction from baseline in MMD in the last 4 weeks of the DBTP; change from baseline in monthly acute migraine-specific medication treatment days in the last 4 weeks of the DBTP; achievement of at least a 5-point reduction from baseline on average impact on everyday activities domain scores over the last 4 weeks of the DBTP as measured by the MPFID; and achievement of at least a 5-point reduction from baseline on average physical impairment domain scores over the last 4 weeks of the DBTP as measured by the MPFID. A sequential testing procedure, specifically, the hierarchical gate-keeping procedures and Hochberg method, was used to maintain the 2-sided study-wise type I error at 0.05 between the primary and secondary endpoints.

Between July 2015 and July 2016, 577 subjects were randomized in a 1:1 ratio to receive placebo (291 subjects) or erenumab 70 mg (286 subjects) monthly by subcutaneous injection for the duration of the 12-week DBTP. A total of 570 subjects were included in the Efficacy Analysis Set.

There was a statistically significant greater reduction in the change in MMD from baseline to the last month of the 12-week DBTP for erenumab 70 mg as compared with placebo. The LSM difference (95% CI) was -1.04 (-1.61, -0.47) days for erenumab 70 mg vs placebo ($p < 0.001$).

The proportion of subjects who achieved at least a 50% reduction in MMD from baseline to the last month of the 12-week DBTP was 29.5% for the placebo group and 39.7% for the

erenumab 70-mg treatment group; results were statistically significant for the erenumab 70-mg group vs placebo (odds ratio = 1.59; 95% CI: 1.12 to 2.27; p = 0.010).

There was a statistically significant greater reduction in the change from baseline in monthly acute migraine-specific medication treatment days in the last month of the 12-week DBTP for erenumab 70 mg as compared with placebo. The LSM difference (95% CI) was -0.59 (-0.96, -0.21) days for erenumab 70 mg vs placebo (p = 0.002).

The proportion of subjects who achieved at least a 5-point reduction from baseline to the last month of the DBTP in the average impact on everyday activities domain scores by MPFID was numerically larger for erenumab 70 mg (40.4%) compared to placebo (35.8%), but the difference was not statistically significant (odds ratio = 1.22; 95% CI: 0.87 to 1.71; p = 0.26).

The proportion of subjects who achieved at least a 5-point reduction from baseline to the last month of the double-blind treatment phase in the average physical impairment domain scores by MPFID was numerically larger for erenumab 70 mg (33.0%) compared to placebo (27.1%), but the difference was not statistically significant (odds ratio = 1.33; 95% CI: 0.92 to 1.90; p = 0.13).

In summary, Study 20120295 in subjects with chronic migraine and Studies 20120296 and 20120297 in subjects with episodic migraine demonstrated sufficient evidence for the efficacy of erenumab 70 mg compared with placebo in the prophylaxis of migraine in adults. In addition, Studies 20120295 and 20120296 also provided sufficient evidence for the efficacy of erenumab 140 mg for prophylaxis of migraine in adults.

2.4.2 Safety Results

Major adverse events include hypersensitivity, injection site reactions, muscle spasm and constipation. Since patients with major cardiovascular events were excluded from pivotal studies, the safety profile is not explored in this population.

2.5 Bridging Study Evaluation

After single dosing 70 mg in healthy Japanese, the C_{max} and AUC_{inf} of erenumab were 1.02-fold and 1.12-fold in non-Asian (within study). After single dosing 140 mg in healthy Japanese, the C_{max} and AUC_{inf} of erenumab were 1.37-fold and 1.39-fold in non-Asian (cross-study). There was no apparent difference in PK parameters between healthy subjects and migraine subjects.

Considering (1) the inter-subject variation of erenumab was about 25% via SC route and (2) the metabolism pathway of erenumab is via catabolism seldom affected by genetic polymorphism, erenumab is none to minimally ethnically sensitive from between Asian and non-Asian from PK aspect.

The sponsor provided results of a Japanese phase II study 20120309 as bridging data. 475 subjects with episodic migraine were randomized to erenumab 28 mg Q1M, erenumab 70 mg Q1M, erenumab 140 mg Q1M or placebo. The primary endpoint, the difference to placebo of change from baseline in monthly migraine days was -1.25 days for erenumab 28 mg ($p=0.004$), -2.25 days for erenumab 70 mg ($p<0.001$) and -1.89 days ($p<0.001$) for erenumab 140 mg. The safety profile was comparable with that of global trials. In summary, the efficacy results and safety profile 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 erenumab 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

The sponsor should submit the results of the following studies once available.

(1) Study CAMG334A2302 and Study CAMG334A2304 (with subgroup analysis of East Asians)
(2) Japanese phase III trial 20170609

Routine pharmacovigilance should be conducted.