Public Assessment report

Aimovig® (140 mg/ml Solution for Injection)

Erenumab

Submission number: 1C 15044/62(NB)

Applicant: Novartis (Thailand) Ltd.

Product team leader:	Worasuda Yoongthong
Co-product team leader:	Kridiphol Janthranant
Start of the procedure:	19 June 2019
e-submission number and sequence number	e6200041 0000-0002
Date of this report:	13 May 2020

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Administrative information

Invented name of the medicinal product:	Aimovig (140 mg/ml Solution for Injection)
INN (or common name) of the active substance(s):	erenumab
Applicant:	Novartis (Thailand) Ltd.
Applied Indication(s):	Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.
Pharmaco-therapeutic group **(ATC Code):**	Calcitonin gene-related peptide (CGRP) antagonists (N02CD01)
Pharmaceutical form(s) and strength(s):	Solution for Injection Erenumab 140 mg in 1 ml in pre-filled syringe/ pre-filled pen
Product team leader contact person: **Co-Product team leader contact person:**	**Name**: Worasuda Yoongthong Email: worasuda302@gmail.com **Name**: Kridiphol Janthranant Email: kridipholjan.fda@gmail.com

Declaration

This application includes an Active Substance Master File (ASMF):

☑ Yes

☐ No

☐ The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, including the Product Information, unless there are previous contracts and/or agreements with the third party (ies).

☐ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

List of abbreviations

AI/Pen	Auto-injector pen
AMG-334	Erenumab
CGRP	Calcitonin gene-related peptide
EMA	European medicines agency
GMP	Good manufacturing practices
RW	Regular wall
SC	Subcutaneous
STW	Special thin wall
PFS	Prefilled syringe

1. Recommendation

Based on the review of the data and the Applicant's response to the list of questions (LOQs) on quality, safety, efficacy, Thai FDA consider that the application for Aimovig 140 mg/ml Solution for Injection in the treatment of

"Prophylaxis of migraine in adults who have at least 4 migraine days per month."

is approvable provided that the applicant commits to perform a number of post authorisation measures to be reported back to Thai FDA within predefined timeframes. A preliminary list of such post-authorisation measures is in section 5.1 of this report. In order to further confirm the concerned points related to the RMP, the MAHs will provide Study 20120178 -A Phase II, Randomized, Double-blind, Placebo controlled Study to Evaluate the Efficacy and Safety of AMG334 in Migraine Prevention and Non-interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries.

2. Executive summary

2.1. Problem statement

Migraine is a multi-symptom chronic disease characterized by a moderate to severe unilateral throbbing headache lasting from 4 to 72 hours. The symptoms include nausea, vomiting, and sensitivity to light, sound, and head movements. [1] The severe pain and other associated symptoms have been shown to affect a patient's physical and social ability and reduce quality of life. [2, 3]

Migraine pathology involves sensitization and excitation of trigeminal ganglion nerves caused by many neuro-peptides such as substance P, and calcitonin gene-related peptide (CGRP).[1] Calcitonin gene-related peptide (CGRP), greatly expressed in trigeminal neurons, induces edema, increases blood flow, and recruits inflammatory cells, promoting neurogenic inflammation and leading to migraine pain at Peripheral Nervous System. Besides during migraine, CGRP is released centrally at synapses in the trigemino-cervical complex to sensitize neuronal circuits associated with diminution of the neuron activation threshold, leading to allodynia, nausea, photophobia, and phonophobia. CGRP levels are distinctively increased during the headache phase of both migraines with or without aura. [4, 5]

11% of an adult has migraine attack worldwide [6] Medical treatment for migraine is non-specific symptomatic agents such as non-steroidal anti-inflammatory drugs (NSAID) or migraine-specific medications such as triptans or ergotamine derivatives. [7] As a result of epidemiologic studies, pharmacological prophylactic treatment is recommended to be part of the treatment for migraine patients who have high severity of disease characterized by frequent attacks or functional impact

Many of the commonly prescribed prophylaxis treatments were not intentionally developed for preventing migraine, such as antiepileptic drugs, β-blockers and antidepressant. After following the use of these drugs, the result has reviewed that it was lack of efficacy, tolerability and patient adherence. [8] Thus, effective prophylactic therapies for migraine are greatly needed. According to the pathophysiology of migraine, CGRP is a target for migraine preventive therapies. AMG-334 (Erenumab), a human monoclonal immunoglobulin G2, is a potent, selective, full antagonist of the CGRP receptor that consequently inhibits the action of CGRP [9] resulting in reducing the frequency of migraine days. Erenumab, commercially available as Aimovig®, is a recent developed migraine preventive agent for prophylaxis of migraine in adults.

2.2. About the product

Aimovig contains Erenumab which is a potent, selective, full antagonist of the CGRP receptor that consequently inhibits the action of CGRP [9] resulting in reducing the frequency of migraine days. Aimovig 140 mg/ml Solution for Injection is indicated for the preventative treatment of migraine in adults who have at least 4 migraine day with two dose options of 70 mg and 140 mg monthly (every 4 weeks), delivered subcutaneously (SC) as either 1 or 2 injections of 70 mg/mL autoinjector pen (AI/pen) or prefilled syringe (PFS). Aimovig 70 mg/ml was already approved in stringent country

(USFDA and EMA) in 2018 and in Thailand (registered number 1C 15100/62 (NBC), e-identifier 6100037) in 2019 in the same indication as EMA approval.

The 140 mg dose administered as two 1 mL injections of 70 mg/mL in the 2 pivotal migraine studies were included in the original submission (Studies 20120295 and 20120296).

The proposed commercial formulation is AI/pen or PFS with 1-mL injection of 140 mg/mL which supports one subcutaneous injection of 1ml for the 140mg dose in addition to two subcutaneous injections of 1ml 70-mg/mL (AI/pen or PFS) for140 mg dose or single injection of 1ml 70-mg/mL (AI/pen or PFS) for 70 mg dose treatment.

This application concerns a line extension to register an addition of a new strength of 140 mg with the same pharmaceutical form (aqueous solution for subcutaneous), to Aimovig 70 mg (registered number 1C 15100/62 (NBC), e-identifier 6100037). The new solution for injection will be presented in both a pre-filled syringe and a prefilled pen.

2.3. The development programme/compliance with Thai FDA guidance/scientific advice

Not applicable.

2.4. General comments on compliance with GMP, GLP, GCP

The GMP certificate from Amgen Manufacturing Limited is available accepted by Thai FDA. The information stated in the dossier that non-clinical studies and clinical studies were complied with GLP and GCP and already assessed by EMA and acceptable.

2.5. Type of application and other comments on the submitted dossier

- Extension of marketing authorisation

The original product was Aimovig 70 mg Solution for Injection in autoinjector pen (AI/pen) or prefilled syringe (PFS) which was registered in Thailand.

The new strength, Aimovig 140 mg solution for injection, is also an aqueous solution for injection with same pharmaceutical excipients as the approved product, Aimovig 70 mg solution for injection.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Novartis submitted an application for extension of marketing authorization for the addition of new finished product presentation. The currently approved for erenumab finished product include a pre-filled syringe (PFS) and pre-filled auto-injector/pen (AI/pen) containing a 1 mL deliverable volume of 70 mg/mL erenumab solution for subcutaneous injection (Aimovig 70 mg/ml; registered number 1C 15100/62 (NBC), e-identifier 6100037).

The new finished product is presented as Solution for Injections containing 140 mg of erenumab as active substance. Other ingredients are sucrose, polysorbate 80, sodium hydroxide (for pH adjustment), glacial acetic acid, and water for injections.

The product is available in pre-filled syringe or pre-filled pen (1 ml, Type 1 glass) with a stainless-steel needle and a needle cover (rubber containing latex).

3.1.2. Active substance

Erenumab is a human monoclonal immunoglobulin G2 (IgG2) antibody expressed in a Chinese hamster ovary (CHO) cell line. Erenumab specifically binds to the extracellular domain of the calcitonin gene-related peptide receptor (CGRP-R) and prevents its interaction with the neuropeptide CGRP.
Details of active substance remain unchanged compared to the original erenumab application for Aimovig (70 mg/mL Solution for injection) registered number 1C 15100/62 (NBC), e-identifier 6100037. The applicant submitted Module 1-5 by uploading same documents for approving of Aimovig 70 mg/ml which were evaluated. The additional response data for external experts' comments on Aimovig 70 mg/ml was already submitted also in sequence 0000 of e6200041

The drug substance is manufactured in accordance with current Good Manufacturing Practices (GMP). The facilities involved in the manufacture and testing of erenumab drug substance are provided.

3.1.3. Finished Medicinal Product

Description of the product

The finished product is presented as a sterile, single-use, preservative-free for SC injection in both a PFS and pre-filled AI/Pen. The AI/Pen is a delivery device that provided ready-to-use, pre-assembled with the PFS. The primary container of both container systems is the same, except the PFS uses a regular wall (RW) needle and the AI/Pen uses a special thin wall (STW) needle.

Pharmaceutical development

The applicant has previously developed an Aimovig finished product formulation which contains a 70 mg presentation (70 mg/ml) for subcutaneous administration in either a pre-filled syringe (PFS) or a pre-filled pen/auto-injector (AI). This line extension application concerns a 140 mg presentation (140 mg/ml) of Aimovig including both PFS and pen/AI. The 140 mg presentation includes the same excipients as the 70 mg presentation with slightly different quantities.

Comparability was performed in accordance with ICH Q5E and has been sufficiently demonstrated in the comparison of 140 mg/mL pre-filled syringe and pre-filled pen/AI finished product with 70 mg/ml finished product manufactured at the commercial manufacturing site AML (Juncos, Puerto Rico, USA).

The erenumab 140 mg/ml pre-filled pen (auto-injector) contains a Type 1 glass pre-filled syringe (PFS). There is a slight difference in the auto-injector spring force required for the 140 mg/ml presentation compared to the already approved presentation. However, the pre-filled pen/AI for erenumab 140 mg/ml is the same as the SureClick pre-filled pen/AI that was approved in Thailand and EMA.

Overall, the description of pharmaceutical development is sufficiently comprehensive and justifies the development of formulation composition, manufacturing process and container closure system.

Manufacture of the product and process controls

Manufacturer and site responsibilities

The facilities involved in the manufacture and testing of 140 mg/ml finished product are listed and are the same as the facilities involved in the manufacture and testing of the already approved 70 mg/ml presentation of Aimovig including pre-filled syringe and pre-filled pen/AI.

Manufacturer for Aimovig 140 mg/mL solution for injection in pre-filled syringe

- **Manufacturing/ Primary packaging site**

  Amgen Manufacturing Limited, State Road 31, Km 24.6 Juncos, Puerto Rico 00777-4060, United States of America.

- **Secondary packaging site**

  Amgen Europe B.V, Minervum 7061, 4817ZK Breda, Netherlands.

Manufacturer for Aimovig 140 mg/mL solution for injection in pre-filled pen

- **Manufacturing/ Primary packaging site** (**For pre-filled syringe**)

Amgen Manufacturing Limited, State Road 31, Km 24.6 Juncos, Puerto Rico 00777-4060, United States of America.

- **Secondary packaging site (Principal site for assembly of pre-filled syringe in the autoinjector and secondary packaging for drug product)**

  Amgen Europe B.V, Minervum 7061, 4817ZK Breda, Netherlands.

Confirmation of the GMP status for the manufacturing and testing sites was provided.

Manufacturing process

Acceptable ranges are provided for process parameters and brief process flow diagrams are provided for the manufacturing of finished product as well as for the assembly process of both the pre-filled syringe and the pre-filled pen/AI.

Process control

Performance indicators allow direct assessment of product quality and/or process consistency. Performance indicators are evaluated against predetermined limits during process validation and a subset of performance indicators are designated as in-process control (IPC) parameters for routine manufacture. IPCs which should be controlled within a defined range to ensure final product quality are designated as critical. In addition to IPCs, some in-process tests may be designated as real time release testing (RTRT). IPCs are part of the comprehensive integrated control strategy.

Process validation

The validation data presented demonstrate that the process is robust and performs as intended. Three consecutive commercial scale batches and one engineering run were manufactured to validate the manufacturing process of finished product.

Transportation validation data have also been presented which confirms that the quality attributes are maintained when the finished product is transported within the temperature range of 2 °C to 8 °C.

Furthermore, the applicant has given a justification for not providing further validation data for the pre-filled pen assembly process. The arguments presented are mostly based upon analytical comparability and stability studies for the Aimovig 140 mg/ml pre-filled syringe and pre-filled pen demonstrating no effect on quality for the assembly process as well as the applicants manufacturing experience with similar products produced on the existing commercial manufacturing lines including the already approved 70 mg/ml presentation of Aimovig. The justification provided is found acceptable.

The sterility assurance of the filling process was evaluated and assured through the aseptic process simulation validation (media fill) program. Media fill validation has successfully been performed and completed at AML to support the finished product aseptic process conditions for erenumab. Results and requirements for the media fill validation cover the maximum line speed and duration and are in line with the current EU requirements. This is found acceptable.

Control of excipients

The formulation of the drug product (including sucrose, polysorbate 80, glacial acetic acid, sodium hydroxide and water for injection) comply with the requirements and specifications of the relevant compendial monographs and does not include novel excipients.

The excipients used in the Aimovig 140 mg/mL drug product formulation referred to NF, USP, Ph.Eur., JP There was no novel excipients.

Control of Drug product

Product specification

The methods included in the specifications are the same as those applied for the already approved 70 mg presentation of Aimovig, and the specification limits are essentially identical to those for the 70 mg/mL presentation. The only exceptions are the acceptance criteria for protein concentration and color.

In conclusion, the specifications are found acceptable.

Analytical procedures

The majority of the analytical procedures are identical to the Aimovig 70 mg/mL. The density of erenumab 140 mg/mL is slightly higher than for the Aimovig 70 mg/mL. Therefore, the calculations performed to determine deliverable volume of both the PFS and the AI/Pen differs between the two presentations. The method description of the AI/Pen injection time is updated to refer to the 140 mg/mL (AI/Pen).

No new validation summary reports have been submitted as compared to the dossier of the Aimovig 70 mg/mL. Five qualification/validation methods are compendial methods, and therefore the reports are not required.

The compendial method for subvisible particles is briefly described, and the results are found acceptable. The injection time method was validated for testing the 140 mg/mL (AI/Pen). The validation is briefly described and the results are found acceptable.

Validation/Verification of analytical procedures

Analytical procedures used to test the 140 mg/mL were validated in accordance with ICH Harmonized Tripartite Guide Validation of Analytical procedures: Test and Methodology (Q2(R1)). Compendial methods are appropriately verified for their intended use.

For PFS, the deliverable (extractable) volume measurement is as described in compendia. Validation of analytical procedures is not required for compendial methods. This method has been appropriately verified for its intended application. The contained volume measurement has been demonstrated suitable for use through drug product process validation. The contained volume is converted to deliverable volume by subtracting the container hold-up volume. Both measurements are suitable for the determination of deliverable volume.

For AI/Pen, The validation studies for analytical procedures used to test the prefilled SureClick® autoinjector (AI/Pen) are provided.

The injection time method was validated for testing the 140 mg/mL prefilled SureClick® autoinjector (AI/Pen) samples. The validation demonstrates the suitability of this method for the routine assessment of injection time under actual conditions of use.

Batch analyses

The batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for Aimovig 140 mg/mL.

Characterization of impurities

Characterization results in the Elucidation of Structure and Other Characteristics report can be applied to the 140 mg/mL drug product as there are no differences in formulation or concentration between drug substance and the 140 mg/mL drug product and the difference in formulation and concentration between the 70 mg/mL and 140 mg/mL drug product does not have a significant impact on product quality attributes. The characterization results using drug substance are applicable to the 140 mg/mL drug product as there are no differences in concentration or formulation. The drug product container closure system qualification also demonstrated that there is no impact to product quality.

Product-related Impurities

Although the product-related impurities could have a potential impact on patient safety or product efficacy, they are present only at very low levels in the drug product and are controlled to acceptable levels by the manufacturing process. The risk assessment and overall control strategy for each of these product-related impurities is presented in Integrated Control Strategy report.

Container and Closure System

The primary container closure consists of a 1 mL Type I glass syringe with a stainless-steel staked needle closed with an elastomeric needle shield and a bromobutyl elastomeric plunger stopper laminated with a fluoropolymer film on the product contact surface.

The AI/Pen is a single-use, disposable, handheld, mechanical (spring-based) delivery device which consists of a PFS contained within two subassemblies.

Stability of the product

A shelf-life of 2 years (24 months) when stored at the recommended storage conditions of 5 °C and in-use period of 14 days when stored at up to 30 °C for the drug product is claimed. The shelf-life and storage conditions are identical to the Aimovig 70 mg presentation. This claim is based on stability studies that were carried out in accordance with ICH Q5C and Q1A guidelines.

The ongoing stability program for the PFS finished product includes, to date, 24 to 42 months stability data for primary lots and production lots.

To support the proposed storage for 14 days at room temperature (at up to 30 °C), stability study of the PFS has been performed at 30 °C after storage at the recommended storage condition for 24 months. In addition, stability data has been provided at accelerated (25°C, 30°C) and stressed (40°C) storage conditions. Results have also been presented demonstrating that the secondary packaging effectively protects the finished product from light exposure.

The data obtained to date from the stability program for the AI/Pen finished product includes 12, 6 and 1.25 months stability data for primary lots and production lots at the recommended storage condition. All results met the stability study acceptance criteria as well as the AI/Pen release acceptance criteria.

The proposed shelf-life for the AI/Pen of 24 months at 5°C and 14 days at up to 25°C is, however, mainly justified by the PFS stability data. The stability results for the AI/Pen at the recommended (5 °C), accelerated and stressed conditions are consistent with the PFS. The primary container closure system is identical to that used for the PFS and there is no product contact with the auto-injector device. Comparability between the PFS and the AI/Pen has been shown demonstrating that finished product quality is not impacted by the AI/pen assembly process and extrusion from the device.

The acceptable shelf-life is 24 months (2°C-8°C). The pre-filled syringe and pre-filled pen should be kept in the outer carton in order to protect from light. After removal from the refrigerator, Aimovig must be used within 14 days when stored at room temperature (up to 25°C), or discarded. If it is stored at a higher temperature or for a longer period it must be discarded.

Adventitious agents

The active substance used for the 140 mg/mL presentation is the same as the active substance used for the already approved 70 mg/mL presentation. Therefore, the quality information remains unchanged. This is found acceptable.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

For quality aspect, applicant provide the identical quality data of Aimovig 140 mg/mL as same as Aimovig 70 mg/mL approved product. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. Stability data indicated following the ASEAN guideline ensure to safe use.

No major objections were identified.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The evaluating result of un-redacted assessment report from EMA and the expert committee meeting on 27th June 2019 summarized in the similarly results. Then overall in the quality data on manufacturing and quality control of drug substances and drug product is acceptable. The extension of marketing authorization for Aimovig 140 mg/mL is approvable from the quality point of view.

3.2. Non-clinical aspect

No new clinical data was submitted in this application. The overall evaluation results of non-clinical studies erenumab were provided in the Aimovig 70 mg/ml assessment report for registration (registered number 1C 15100/62 (NBC), e-identifier 6100037). The results of pharmacodynamics and pharmacokinetics studies both in vivo and in vitro generally similar like approved product Aimovig 70 mg/ml. The toxicological test and justified were provided in the Aimovig 70 mg/ml assessment report for registration and it was acceptable.

3.3. Clinical aspects

The clinical trials were performed in accordance with GCP as claimed by applicant.

3.3.1. Tabular overview of clinical studies

Study ID	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Primary Endpoint
20160349	Phase I, randomized, open label	AMG 334 s single 1-mL (140 mg/mL) PFS injection or two 1-mL (70 mg/mL) PFS injections	Bioequivalence, pK, safety, tolerability, and immunogenicity	211 healthy male and female (complete 201) Test (N=105): AMG 334 140 mg (1 x 1 mL 140 mg/mL) prefilled syringe. Ref (N=106): AMG 334 140 mg (2 x 1 mL 70 mg/mL) prefilled syringe	Up to 120 days	Healthy subjects Age: 18-55 years BMI: 19.2-30.4 kg/m^2	C^{max}, AUC^{last} and AUC^{inf}.
20160442	Phase I, randomized, open label	AMG 334 s single 1-mL (140 mg/mL) Prefilled AI/Pen injection or two 1-mL (70 mg/mL) Prefilled AI/Pen injections	Bioequivalence, pK, safety, tolerability, and immunogenicity	104 healthy male and female Test (N=52): AMG 334 140 mg (1 x 1 mL 140 mg/mL) prefilled syringe. Ref (N=52): AMG 334 140 mg (2 x 1 mL 70 mg/mL) prefilled syringe	Up to 120 days	Healthy subjects Age: 18-55 years BMI: 18.4-30.4 kg/m^2	Cmax, AUClast and AUCinf.

Study 20160442 was terminated before planned study completion based on U.S. Food and Drug Administration (FDA) feedback that this study was not necessary to support approval of the 140-mg single-injection delivery system (AI/pen or PFS). The EMA, respectively, agreed that Study 20160349 was appropriate on its own to bridge the new 140mg/mL formulation with currently approved product presentations. Safety data for Study 20160442 were summarized but the pK and anti-erenumab antibody samples collected were not tested and analyses were not conducted.

3.3.2. Pharmacokinetics

The study 20160349 was a multicenter, open-label, randomized, single-dose, parallel group study conducted in healthy to assess the BE, pK, safety, tolerability, and immunogenicity profile of single dose of Aimovig administered by 1 x 140 mg or 2 x 70 mg prefilled syringe SC injection. Blood samples for pharmacokinetic analysis were taken pre-dose and up to 98 days post-dose.

Treatment A (Test): AMG 334 140 mg (1 x 1 mL 140 mg/mL) prefilled syringe.

Treatment B (reference): AMG 334 140 mg (2 x 1 mL 70 mg/mL) prefilled syringe.

The results from the comparative bioavailability study are presented below.

Table 2 - Pharmacokinetic parameters for erenumab (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	Arithmetic	SD
$AUC_{(0-t)}$ (day*µg/mL)	361	121	382	106
$AUC_{(0-\infty)}$ (day*µg/mL)	358	126	381	108
C_{max} (µg/mL)	13.2	4.30	13.6	3.57
T_{max}* (days)	6.0	1.9-11	6.0	0.98-11
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 3 – Statistical analysis for erenumab (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals
$AUC_{(0-t)}$	0.93	0.86-1.10
C_{max}	0.95	0.88-1.03

Bioequivalence was demonstrated for the primary parameters AUC0-t and Cmax.

3.3.3. Pharmacodynamics

Immunogenicity

From study 20160349, no subjects had binding or neutralizing antibodies at baseline.

Development of binding antibodies against erenumab was observed in 35 subjects (16.9%) post-baseline in the total erenumab group, including 16 subjects (15.8%) in the erenumab 1 x 1 mL 140-mg/mL PFS (test) group and 19 subjects (17.9%) in the erenumab 2 x 1 mL 70-mg/mL PFS (reference) group. Of the 35 subjects that tested positive for binding antibodies, 4 were transient (i.e., negative result at the last time point tested).

Neutralizing antibodies against erenumab developed in 1 subject (0.5%) after administration of erenumab 2 x 1 mL 70-mg/mL PFS; the subject was positive for anti-erenumab neutralizing antibodies at the end of study visit, but reverted to neutralizing antibody negative at the 3-month antibody follow-up. No notable differences in the development of anti-erenumab antibodies between the 2 treatment groups were observed.

The presence of anti-erenumab antibodies was not associated with immune disorder-related adverse events. Mean AUCinf values in anti-erenumab antibody positive subjects were within the range of antibody negative subjects. This is in accordance with results from the original application. The incidence of ADAs was 16.9% in the total erenumab 140 mg treated group which is higher compared

to that in the studies in the original. It is noted that the same immunoassays as in the original application were used.

Study 20160442: Blood sample were collected, but analysis of ADAs was not performed.

3.3.4. Discussion on clinical pharmacology

This line extension concerns a new strength of Aimovig, 140 mg to be administered as a single monthly injection. The drug product consists of a solution of injection filled in either a pre-filled syringe (PFS) or an autoinjector pen (AI/pen). Study 20160349, in which the bioavailability of the new 140 mg PFS was compared to the already approved PFS given as 2x70 mg, is pivotal for the application.

Study 20160442 in which the bioavailability of the AI/pen was evaluated was terminated early and only safety results were reported. The PK samples were not analyzed and thus bioequivalence not evaluated. The PFS and the AI/pen are both filled with the same solution for injection. It is therefore considered sufficient to establish bioequivalence with the PFS only. In the original application bioequivalence was demonstrated between the 70 mg PFS and AI/pen, which further supports that a study with the PFS is sufficient.

The pivotal study 20160349 and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated. The 90% CI of the test/reference ratio for both AUClast and Cmax was within the conventional acceptance range for bioequivalence, 80.00-125.00%. Hence, the new 140 mg prefilled syringe is considered bioequivalent to 2x70 mg of the already approved prefilled syringe.

Development of binding antibodies against erenumab and neutralizing antibodies against erenumab were similar between the 1 x 1 mL 140-mg/mL PFS (test) group and 2 x 1 mL 70-mg/mL PFS (reference) group. The presence of ADA did not influence the exposure of AMG334. This is in accordance with results from the original application. The incidence of ADAs was 17.9% in study 20160349 which is somewhat higher compared to that in the original application. The incidence of ADAs during the double-blind treatment phase of the clinical studies is 6.3% (56/884) among subjects receiving a 140 mg dose of erenumab and 2.6% (13/504) among subjects receiving a 140 mg of erenumab.

3.3.5. Conclusion on clinical pharmacology

Pharmacokinetic and Pharmacodynamics studies were performed in concordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) that complete and appropriate. Based on the comparative bioavailability study (20160349) the new 140 mg/mL prefilled syringe was bioequivalent to 2x70 mg/mL of the already approved product prefilled syringe. The result of study 20160349 can be extrapolated to the 140 mg/mL AI/Pen. The incidence of ADAs was 17.9% in study 20160349 which is somewhat higher compared to that in the original application. No new safety concern of immunogenicity was identified based on the ADA data submitted in this application.

3.3.6. Clinical efficacy and safety

Summary of main efficacy and safety results

No new clinical efficacy studies of erenumab administered as a single 140-mg/mL dose by PFS or AI/pen delivery system were conducted for this line extension application. The 140 mg dose administered as two 1 mL injections of 70 mg/mL in the 2 pivotal migraine studies were included in the original submission (Studies 20120295 and 20120296). Since the posology for Aimovig will not be changed, a new efficacy study is not required.

For safety results, the results were derived from 2 BE studies conducted to evaluate bioequivalence of Aimovig 140 mg/ml in PFS and AI/Pen with Aimovig 70 mg/mL in PFS and AI/Pen. The overall incidence of treatment-emergent AEs collected in the single dose bioequivalent studies 20160349 and 20160442 is summarized in table below.

Table 7 – Summary of Subject Incidence of adverse Events in Studies 20160349 and 20160442 (Safety Analysis Set)

	Study 20160349 Erenumab-aooe 140 mg PFS SC			Study 20160442[a] Erenumab-aooe 140 mg AI/pen SC		
	2 x 1 mL 70 mg/mL (N = 106) n (%)	1 x 1 mL 140 mg/mL (N = 105) n (%)	Total (N = 211) n (%)	2 x 1 mL 70 mg/mL (N = 52) n (%)	1 x 1 mL 140 mg/mL (N = 52) n (%)	Total (N = 104) n (%)
All treatment-emergent adverse events - n (%)	35 (33.0)	31 (29.5)	66 (31.3)	17 (32.7)	12 (23.1)	29 (27.9)
Grade ≥ 2 adverse events	8 (7.5)	8 (7.6)	16 (7.6)	7 (13.5)	2 (3.8)	9 (8.7)
Grade ≥ 3 adverse events	0 (0.0)	1 (1.0)	1 (0.5)	1 (1.9)	0 (0.0)	1 (1.0)
Grade ≥ 4 adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.0)
Serious adverse events	1 (0.9)	2 (1.9)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Device-related treatment-emergent adverse events - n (%)	1 (0.9)	1 (1.0)	2 (0.9)	4 (7.7)	4 (7.7)	8 (7.7)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AI/pen = autoinjector pen; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects reporting at least 1 occurrence of an adverse event; N = number of subjects in the analysis set; PFS = prefilled syringe; SC = subcutaneous

For both studies, the safety analysis set consisted of all randomized subjects who received investigational product.

Coded using MedDRA version 20.0 (Study 20160349) and MedDRA version 20.1 (Study 20160442).

Graded using CTCAE version 4.0.

[a] Study 20160442 was terminated early following confirmation that the data was not required to support approval of the 140-mg/mL PFS or AI/pen drug product presentation (refer to Section 1.1.1 for details).

Source: Table 12-1 and Table 14-6.2.3 of Study 20160349 CSR; Table 14-6.1.1 and Table 14-6.4.1 of Study 20160442 CSR

Table 8 – Treatment-emergent Adverse Events by Preferred Term Occurring in ≥ 2 Subjects in the Total Erenumab-aooe Group of Study 20160349 and Study 20160442 (Safety Analysis Set)

	Study 20160349 Erenumab-aooe 140 mg PFS SC			Study 20160442[a] Erenumab-aooe 140 mg AI/pen SC		
	2 x 1 mL 70 mg/mL (N = 106) n (%)	1 x 1 mL 140 mg/mL (N = 105) n (%)	Total (N = 211) n (%)	2 x 1 mL 70 mg/mL (N = 52) n (%)	1 x 1 mL 140 mg/mL (N = 52) n (%)	Total (N = 104) n (%)
Number of subjects reporting treatment-emergent adverse events	35 (33.0)	31 (29.5)	66 (31.3)	17 (32.7)	12 (23.1)	29 (27.9)
Headache	6 (5.7)	10 (9.5)	16 (7.6)	5 (9.6)	3 (5.8)	8 (7.7)
Upper respiratory tract infection	7 (6.6)	8 (7.6)	15 (7.1)	2 (3.8)	0 (0.0)	2 (1.9)
Pain in extremity	3 (2.8)	1 (1.0)	4 (1.9)	- (-)	- (-)	- (-)
Dizziness	2 (1.9)	1 (1.0)	3 (1.4)	- (-)	- (-)	- (-)
Nasal congestion	2 (1.9)	1 (1.0)	3 (1.4)	- (-)	- (-)	- (-)
Nausea	2 (1.9)	1 (1.0)	3 (1.4)	1 (1.9)	1 (1.9)	2 (1.9)
Skin abrasion	2 (1.9)	1 (1.0)	3 (1.4)	- (-)	- (-)	- (-)
Toothache	2 (1.9)	1 (1.0)	3 (1.4)	1 (1.9)	0 (0.0)	1 (1.0)
Anxiety	0 (0.0)	2 (1.9)	2 (0.9)	- (-)	- (-)	- (-)
Back pain	0 (0.0)	2 (1.9)	2 (0.9)	0 (0.0)	1 (1.9)	1 (1.0)
Blood creatine phosphokinase increased	0 (0.0)	2 (1.9)	2 (0.9)	1 (1.9)	0 (0.0)	1 (1.0)
Constipation	0 (0.0)	2 (1.9)	2 (0.9)	- (-)	- (-)	- (-)
Injection site hemorrhage	1 (0.9)	1 (1.0)	2 (0.9)	1 (1.9)	4 (7.7)	5 (4.8)
Injection site pain	0 (0.0)	2 (1.9)	2 (0.9)	3 (5.8)	0 (0.0)	3 (2.9)
Laceration	2 (1.9)	0 (0.0)	2 (0.9)	1 (1.9)	1 (1.9)	2 (1.9)
Viral upper respiratory tract infection	2 (1.9)	0 (0.0)	2 (0.9)	- (-)	- (-)	- (-)
Vessel puncture site haemorrhage	- (-)	- (-)	- (-)	1 (1.9)	2 (3.8)	3 (2.9)
Cough	- (-)	- (-)	- (-)	1 (1.9)	1 (1.9)	2 (1.9)
Neutropenia	- (-)	- (-)	- (-)	2 (3.8)	0 (0.0)	2 (1.9)
Rhinitis allergic	0 (0.0)	1 (1.0)	1 (0.5)	2 (3.8)	0 (0.0)	2 (1.9)

In general, treatment-emergent adverse events and the frequency of these AEs were similar across treatment groups in study 20160349. Among the treatment-emergent Adverse Events reported by Preferred Term Occurring in 2 Subjects (Study 20160349 and Study 20160442), constipation and injection site reactions has already been identified as ADR and is listed in SmPC 4.8. Device-related Adverse Events/Injection site reactions are described in the section below.

In study 20160349, No fatal adverse events were reported. Serious adverse events were reported by 3 subjects (1.4%), including 2 subjects (1.9%) in the 1 x 1 mL 140 mg/mL PFS (test) group and 1 subject (0.9%) in the 2 x 1 mL 70 mg/mL PFS (reference) group. In addition, study 20160442 have no serious or fatal adverse events were reported.

A case of drug-induced liver injury was reported from study 20160349. This event was initially reported as an SAE of acute liver failure and later was updated by the investigator to drug induced liver injury due to investigator's concern related to concomitant medications (namely Augmentin, taken for 10 days, approximately 6 weeks prior to liver enzyme elevations; the subject had also taken

chlordiazepoxide). The investigator's final causality assessment was not related to Aimovig. The subject completed the study.

For other SAEs, two serious adverse events from study 20160349 were reported which included a 35-year-old male experienced left side hearing loss and laceration left axilla after a motor vehicle accident while driving. The events resolved after treatment. The investigator considered the SAEs was not related to both Aimovig and the device and the subject completed the study; a 24-year-old male experienced left-hand septic arthritis, metacarpophalangeal joint and cellulitis following an infection secondary to a spider bite. The events resolved after treatment. The investigator considered the SAEs was not related to both Aimovig and the device and the subject completed the study.

For laboratory findings, data from serum chemistry, haematology laboratory values in general were consistent with the original marketing application dossier. The subject with abnormal lab values at or above CTCAE grade 3 and one SAE were reviewed.

For vital signs, based on the review of the vital signs data for systolic and diastolic blood pressure, heart and respiratory rates, and temperature provided in the CSR, no new safety concerns were identified.

For device-related adverse events/ injection site reactions, in study 20160349; 5 subjects were detected. Injection site reaction events included injection site hemorrhage, injection site pain and injection site swelling. None of these EENTS were considered serious and all were mild in severity (CTCAE grade 1). In study 20160442 found 12 subjects got the adverse events. Injection site reaction events included injection site hemorrhage in 5 subjects, injection site pain in 3 subjects, vessel puncture site hemorrhage in 3 subjects, and injection site bruising, injection site rash, and injection site reaction (1 subject of each). None of these events were considered serious and all were mild in severity (CTCAE grade 1). The overall incidence of injection site reactions was the same for each formulation

Using in pregnancy and lactation, across the clinical development program, a total of 34 pregnancies have been reported in which subjects or their partners were exposed to erenumab or blinded investigational product before or during pregnancy.

Table 10 – Cumulative Birth outcomes for Pregnancies in the Erenumab-aooe Clinical Program Through 31 January 2018

Birth Outcomes	Maternal Exposures	Paternal Exposures
Full-term birth without complications	7	0
Live birth, normal	3	2
Delivered NOS	0	1
Full-term birth with complications	1[a]	0
Preterm birth without complications	1	1
Elective termination NOS	3	0
Spontaneous abortion NOS	2	0
Unknown	3	0
Lost to follow-up	8	2
Total	28	6

NOS = not otherwise specified
Pregnancies in subjects who were unblinded as having received placebo are not included in cumulative tabulations.
[a] Subject 17866027015: the baby had no reported birth complications or congenital anomalies but was admitted to the neonatal intensive care unit for 4 days. The reason for admission was not provided.

There have been no reports of infants receiving breast milk from mothers who were being treated with erenumab.

In Study 20160349, there were 4 pregnancies reported in 3 subjects. One subject had 2 pregnancies: the first pregnancy was electively terminated, and the outcome of the subsequent pregnancy was lost to follow-up. For the remaining 2 subjects, 1 pregnancy was lost to follow-up (last contact indicated elective termination was planned), and the remaining pregnancy outcome was unknown with an

anticipated date of delivery in March 2018. Narratives for pregnancies from Study 20160349 are also provided.

In Study 20160442, no pregnancies were reported.

Overall, the numbers of pregnancies, information and outcomes reported are too limited to evaluate and conclude on the effects of erenumab on pregnancies.

3.3.7. Discussion on clinical safety

The new safety data were derived from the Phase 1 Study 20160349 evaluating the safety, tolerability, immunogenicity profile, and PK of a single SC dose of 140 mg erenumab delivered by PFS as either 1 injection of 140 mg (test) or 2 injections of 70 mg (reference) to healthy volunteers. The safety population included 211 subjects. In addition, safety data from a terminated phase 1 study (Study 20160442) were included in the submission. This study was similar to 20160349 except that erenumab 140 mg was delivered by prefilled AI/pen. The safety population included 104 subjects.

In study 20160349, treatment-emergent adverse events were similar across treatment groups and were reported in 33.0% and 29.5% of subjects in the Aimovig 140 mg (2 x 1 mL 70 mg/mL) and Aimovig 140 mg (1 x 1 mL 140 mg/mL) groups respectively. The most common treatment-emergent AEs were headache, upper respiratory tract infection, and pain in extremity. Most AEs were mild or moderate in intensity. SAEs were reported in 1 (0.9%) and 2 (1.9%) subjects in the respective groups.

One subject in the Aimovig 140 mg (1 x 1 mL 140 mg/mL) group with normal baseline aminotransferase experienced an SAE of drug-induced liver injury. The subject developed grade 4 ALT and AST elevations at day 10 after a single dose of AMG 140mg. The subject did not meet the criteria for Hy's Law. This case was reviewed in detail given the close temporal relationship between the administration of Aimovig and the onset of the events. However, confounding factors were identified including concomitant medications (such as coamoxicillin/clavulanate and chlordiazepoxide) and medical history which precluded drawing conclusions on causality.

In the original application for Aimovig, a small number of subjects with normal baseline LFTs showed elevations to > 3 times ULN or > 5 times ULN during the 12-month Aimovig treatment period. It was recommended that the risk of increased hepatic enzymes should be further monitored and continue to collect the necessary information on reported suspected adverse liver reactions with established PV practices. This is considered acceptable at the current stage and this issue will be further monitored.

In study 20160442, treatment-emergent AEs were reported in 32.7% and 23.1% of subjects in the AMG 334 140 mg (2 x 1 mL 70 mg/mL) and AMG 334 140 mg (1 x 1 mL 140 mg/mL) groups, respectively.

Overall, treatment-emergent adverse events were similar between treatment groups. The most frequently reported AEs were headache (5 subjects [4.8%] overall) and nausea (2 subjects [1.9%]). No SAEs were reported.

In both studies, there were subjects who reported increased blood creatinine phosphokinase after receiving 140 mg treatment (1 x 1 mL 140 mg/mL AI/pen or 2 x 1 mL 70 mg/mL AI/pen). In total, 5 of the 315 subjects treated with erenumab reported Grade 3 (4 subjects) or Grade 4 (1) elevations. This should be further monitored in line with the recommendation of the original application.

Device-related AEs and injection site reactions were generally similar between the erenumab (2 x 1-mL 70 mg/mL) and the erenumab (1 x 1-mL 140 mg/mL) groups.

The results of the comparative study (20160349) demonstrated that development of binding antibodies against erenumab and neutralizing antibodies against erenumab were similar between the 1 x 1 mL 140 mg/mL PFS (test) group and 2 x 1 mL 70 mg/mL PFS (reference) group. The presence of ADA did not influence the exposure of Aimovig. This is in accordance with results from the original application. However, the incidence of ADAs was 17.9% in the present study which is somewhat higher compared to 6.7% (56/884) among the subjects receiving a 70mg dose of erenumab and 2.6% (13/504) among subjects receiving a 140mg dose of erenumab in the original application although the same immunoassay was used. No new safety concern of immunogenicity was identified based on the ADA data submitted in this application. It is considered that the overall incidence of ADAs for Aimovig specified in the Current SmPC does not evoke new safety concerns.

3.3.8. Conclusion on the clinical safety

Studies 20160349 and 20160442 were submitted to support a line extension for the addition of a new strength of 140 mg, to Aimovig 70 mg. The safety data from these studies is consistent with the original application and no new concerns have been identified.

The list of questions (LOQs) was raised by experts in clinical part and the participated experts in the Expert Meeting on 27th June 2019. LOQs were summarized and adequate response by the applicants. Based on the information in dossier and adequate response from the applicant, the clinical part of erenumab is acceptable and appropriate.

3.3.9. Pharmacovigilance system and risk management plan

The Pharmacovigilance system and Risk Management Plan were provided in the eCTD 1.8 Information relating to Pharmacovigilance. The risk specifications, risk minimization measures, and pharmacovigilance system were used the same protocol as Aimovig 70 mg/mL solution for injection in EU Risk Management Plan. The details were summarized as the following tables:

Table: Summary of safety concerns

Important identified risks	None
Important potential risks	Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension
Missing information	Use in pregnant women (including those at risk of pre-eclampsia) Long-term safety

Pharmacovigilance plan

Summary Table of Ongoing and Planned Additional Pharmacovigilance Activities

Study status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due date**
Category 3 – Required additional pharmacovigilance activities				
NIS – A Non-	The following will be estimated: - Number of migraine	Cardiovascular outcomes in		

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due date
Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries Study status: Planned	patients prescribed with a migraine prophylactic drug (with and without CV History) - Number of pregnant migraine patients prescribed with erenumab and other prophylactic treatments - Pattern of utilization (prescriber, length of treatment, switching) - General characteristics and clinical features of migraine patients prescribed prophylactic drug - Exploratory: rates of CV events.	patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension. Use in pregnant women (including those at risk of pre-eclampsia)	Final report submission	End of data collection + 1 year
20120178 - A Phase II, Randomized, Double-blind, Placebo controlled Study to Evaluate the Efficacy and Safety of AMG334 in Migraine Prevention This study includes a 5-year extension for long-term safety data Collection. Study status: Ongoing	To collect long-term safety data for safety of erenumab in Migraine Prevention	Long-term safety	Final report submission:	Q4-2020

Risk minimization measures

Summary Table of Pharmacovigilance and Risk Minimization Activities

	Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks	None	None	None
Important potential risks	Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient	Routine risk minimization Measures: SmPC Section 5.1 (Pharmacodynamics	Routine pharmacovigilance activities beyond ADRs reporting and signal

	Safety concern	Risk minimization measures	Pharmacovigilance activities
	ischemic attack, angina unstable and poorly controlled hypertension	Properties) SmPC Section 4.4 (Special warnings and precautions for use) Additional risk minimization measures: None	detection: None Additional pharmacovigilance activities: NIS - A Non-Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries.
Missing information	Use in pregnant women (including those at risk of Pre-eclampsia)	Routine risk minimization Measures: SmPC Section 4.6 (Fertility, pregnancy and lactation) Additional risk minimization Measures: None	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: Intensive monitoring of pregnancy outcomes Additional pharmacovigilance activities: NIS - A Non-Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries.
Missing information	Long-term safety	No risk minimization measures	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: None Additional pharmacovigilance activities: 20120178 – A Phase 2, Randomized, Double-blind, Placebo controlled Study to Evaluate the Efficacy and Safety of AMG334 in Migraine Prevention This study includes a 5-year extension for long-

	Safety concern	Risk minimization measures	Pharmacovigilance activities
			term safety data collection.

For the detail of this section, please refer to Appendix 6.1.

4. Benefit risk assessment

4.1. Benefits

Erenumab (AMG 334), Aimovig, is indicated for the preventative treatment of migraine in adults who have at least 4 migraine days per month. There are 2 dose options of 70 mg and 140 mg monthly (every 4 weeks), delivered subcutaneously (SC) as either 1 or 2 injections, respectively, of 70 mg/mL auto-injector (AI/Pen).

The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks.

To avoid 2 separate injections for the 140 mg erenumab dose, a single-injection delivery system (AI/pen or PFS) has been developed.

The recommended dose for Aimovig is the same as that already approved for Aimovig in EU and the proposed indication is identical with approved indication in EU and Thailand.

Based on the bioavailability study (20160349), the new 140 mg prefilled syringe was bioequivalent to 2x70 mg of the already approved prefilled syringe. The results of study 20160349 can be extrapolated to the 140 mg auto-injector pen. The 140 mg dose administered as two 1 mL injections of 70 mg/mL in the 2 pivotal migraine studies were included in the original submission (Studies 20120295 and 20120296).

No new efficacy studies were conducted. The efficacy profile of Aimovig remains unchanged.

4.2. Risks

Overall, the results from Study 20160349 and Study 20160442 are quite consistent with the safety demonstrated in the original application.

Study 20160349: injection site reaction events were reported in 5 subjects who included injection site hemorrhage, injection site pain and injection site swelling all were mild in severity.

Study 20160442: injection site reaction events were reported in 12 subjects who included injection site hemorrhage, injection site pain, vessel puncture site hemorrhage, and injection site bruising, injection site rash, and injection site reaction. All were mild in severity.

Among the treatment-emergent Adverse Events reported by Preferred Term Occurring in $\geq$ 2 Subjects (Study 20160349 and Study 20160442), constipation was reported in 2 subjects (1.9%) in the erenumab 1 x 1 mL 140-mg/mL PFS in Study 20160349.

4.3. Benefit-risk balance

This line extension concerns a new strength of Aimovig, 140 mg to be administered as a single monthly injection. Based on the assessment of the pivotal study 20160349, it is concluded that the new 140 mg prefilled syringe is considered bioequivalent to 2x70 mg of the already approved prefilled syringe. The results of study 20160349 can be extrapolated to the 140 mg auto-injector pen.

No major objections were identified that would preclude this extension of marketing authorization from quality perspective and this line extension of Aimovig is approvable from the quality point of view.

The safety profile from Study 20160349 and Study 20160442 are quite consistent with the safety demonstrated in the original application. No new safety concerns were identified.

The proposed indication and recommended dose for Aimovig is the same as that already approved for Aimovig in EU. In principle, provided data are considered to support the approval of Aimovig 1ml 140mg/ml formulation in addition to the already approved Aimovig 1ml 70mg/ml.

Based on the data from quality, non-clinic, and clinical aspects, the benefit-risk balance is positive.

5. Conditions for marketing authorisation and product information

5.1. Conditions for the marketing authorisation

Aimovig 140 mg/mL Solution for injection has the important conditions for the marketing authorisation:

1) Utilized under the health facility and specified on the label

2) Perform PIL usability testing within 12 months after authorisation and report to Thai FDA

3) Monitor the safety of medicine as the protocol in SMP

4) Complied to the risk management plan as the information in section 1.8.2 Risk management system in eCTD

5.2. Summary of product characteristics (SmPC)

The SmPC of Aimovig (140 mg/ml Solution for Injection) was provided in appropriate contents and format that in accordance with Aimovig 70 mg/mL Solution for injection approved by EMA and ThaiFDA. The scientific contents were the latest revision and appropriate. The administrative contents were reflecting as the contents in eCTD and appropriate. SmPC of Aimovig (140 mg/ml Solution for Injection) is available as the attachment in Appendix 6.2.

5.3. Labelling

The data in unit carton from Novartis (Thailand) Ltd. meets the criteria for readability as set out in the standard of Thai FDA 2009 Guideline for Leaflet Development and ASEAN Harmonization.

Unit carton

No.	Topic	Yes	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Country's Registration Number	✓	✓
11	Name and address of Marketing Authorization Holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labelling	✓	✓
14	Recommended Daily Allowance (Vitamins and minerals)	N/A	N/A
15	Warning (as indicated by Ministerial Announcement)	N/A	N/A
16	Pack sizes	✓	✓

✓ Suitable data
X unavailable / inappropriate
N/A Not available or not applicable

Inner label

No.	Topic	Yes	Appropriate
1	Product name	✓	✓
2	Dosage form*	N/A	N/A
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date*	N/A	N/A
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition*	N/A	N/A
10	Country's Registration Number*	N/A	N/A
11	Name and address of Marketing Authorization Holder*	N/A	N/A
12	Name and address of manufacturer*	N/A	N/A
13	Special labelling*	N/A	N/A
14	Recommended Daily Allowance (Vitamins and minerals)*	N/A	N/A
15	Warning (as indicated by Ministerial Announcement)*	N/A	N/A
16	Pack sizes	✓	✓

✓ Suitable data
X unavailable / inappropriate
N/A not available or not applicable
* exempted for small ampoule and vial

5.4. Patient information leaflet (PIL)

The content and format of PIL complied with Thai FDA guideline for leaflet development (3 Jul 2013), as well as the Guideline for Leaflet Development (May 2019) implemented by Division of Innovative Health Products and Services. In addition, this PIL is identical with the PIL of Aimovig (70 mg/mL solution for injection) approved by ThaiFDA in 2019 and add the new strength content for further use the same SmPC in both strengths. However, the applicant must commit for usability testing to ensure that PIL is legible, clear, and easy to understand.

6. Appendices

6.1. Risk management system

Risk management system was available as the attachment.

05_RMP_Aimovig 140 mg.pdf

6.2. PIL, SmPC, and labels

PIL

The PIL and the IFUs of Aimovig (140 mg/mL solution for injection) are available as the attachments.

06_PIL Aimovig 140 mg.pdf

06_PIL_Aimovig 140 mg PFS_(Thai IFU).pc

06_PIL_ Aimovig 140 mg Pen_(Thai IFU).pc

06_PIL_ Aimovig 140 mg PFS_(IFU).pdf

06_PIL_ Aimovig 140 mg Pen_(IFU).pdf

SmPC

The SmPC of Aimovig (140 mg/mL solution for injection) was checked. Contents are correlated with the SmPC of Aimovig 70 mg/mL and 140 mg/mL approved from EMA updated version in 21/2/2020. The SmPC is avialable as the attachment.

07_SmPC_Aimovig 140 mg.pdf

Labels

The labels of Aimovig 140 mg/mL both PFS and AI/Pen are available as the attachments.

08_Labelling_Aimovig 140 mg.pdf

6.3. List of questions (LOQs) and Responses

LOQs and responses of Aimovig (140 mg/mL solution for injection) were available as the attachment.

Aimovig 140 mg_1st Response.pdf

Aimovig 140 mg_2nd Response.pdf

The record of Expert Meeting on 27th June 2019

รายงานการประชุม พิจารณาคำขอขึ้นทะเบี

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