4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine.

Posology

Treatment is intended for patients with at least 4 migraine days per month when initiating treatment with erenumab.

The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks (see section 5.1).

Each 140 mg dose is given either as one subcutaneous injection of 140 mg or as two subcutaneous injections of 70 mg.

Clinical studies have demonstrated that the majority of patients responding to therapy showed clinical benefit within 3 months. Consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter.

Special populations
Elderly (aged 65 years and over)
Aimovig has not been studied in elderly patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age.

Renal impairment / hepatic impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Aimovig in children below the age of 18 years have not yet been established. No data are available.

Method of administration

Aimovig is for subcutaneous use.

Aimovig is intended for patient self-administration after proper training. The injections can also be given by another individual who has been appropriately instructed. The injection can be administered into the abdomen, thigh or into the outer area of the upper arm (the arm should be used only if the injection is being given by a person other than the patient; see section 5.2). Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard.

Pre-filled syringe
The entire contents of the Aimovig pre-filled syringe should be injected. Each pre-filled syringe is for single use only and designed to deliver the entire contents with no residual content remaining.

Comprehensive instructions for administration are given in the instructions for use in the package leaflet.

Pre-filled pen
The entire contents of the Aimovig pre-filled pen should be injected. Each pre-filled pen is for single use only and designed to deliver the entire contents with no residual content remaining.

Comprehensive instructions for administration are given in the instructions for use in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Cardiovascular effect

Patients with certain major cardiovascular diseases were excluded from clinical studies (see section 5.1). No safety data are available in these patients.

Hypersensitivity reactions

Serious hypersensitivity reactions, including rash, angioedema, and anaphylactic reactions, have been reported with erenumab in post-marketing experience. These reactions may occur within minutes, although some may occur more than one week after treatment. In that context, patients should be warned about the symptoms associated with hypersensitivity reactions. If a serious or severe hypersensitivity reaction occurs, appropriate therapy should be initiated and treatment with erenumab should be discontinued (see section 4.3).

Constipation

Constipation is a common adverse reaction of erenumab and is usually mild or moderate in intensity. In a majority of the cases, the onset was reported after the first dose of erenumab; however patients have also experienced constipation later on in the treatment. In most cases constipation resolved within three months. In the post-marketing setting, constipation with serious complications has been reported with erenumab. In some of these cases hospitalisation was required, including cases where surgery was necessary. History of constipation or the concurrent use of medicinal products associated with decreased gastrointestinal motility may increase the risk for more severe constipation and the potential for constipation-related complications. Patients should be warned about the risk of constipation and advised to seek medical attention in case constipation does not resolve or worsens. Patients should seek medical attention immediately if they develop severe constipation. Constipation should be managed promptly as clinically appropriate. For severe constipation, discontinuation of treatment should be considered.

Latex-sensitive individuals

The removable cap of this medicinal product contains latex rubber. May cause severe allergic reactions.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies. No interaction with oral contraceptives (ethinyl estradiol/norgestimate) or sumatriptan was observed in studies with healthy volunteers.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are a limited amount of data from the use of erenumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Aimovig during pregnancy.

Breast-feeding

It is unknown whether erenumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, use of Aimovig could be considered during breast-feeding only if clinically needed.

Fertility

Animal studies showed no impact on female and male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Aimovig is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

A total of over 2 500 patients (more than 2 600 patient years) have been treated with Aimovig in registration studies. Of these, more than 1 300 patients were exposed for at least 12 months and 218 patients were exposed for 5 years. The overall safety profile of Aimovig remained consistent for 5 years of long-term open-label treatment.

The reported adverse drug reactions for 70 mg and 140 mg were injection site reactions (5.6%/4.5%), constipation (1.3%/3.2%), muscle spasms (0.1%/2.0%) and pruritus (0.7%/1.8%). Most of the reactions were mild or moderate in severity. Less than 2% of patients in these studies discontinued due to adverse reactions.

Tabulated list of adverse reactions

Table 1 lists all adverse drug reactions that occurred in Aimovig-treated patients during the 12-week placebo-controlled periods of the studies, as well as in the post-marketing setting. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from the available data).

Table 1 List of adverse reactions

System Organ Class	Adverse reaction	Frequency category
Immune system disorders	Hypersensitivity reactions[a] including anaphylaxis, angioedema, rash, swelling/oedema and urticaria	Common
Gastrointestinal disorders	Constipation	Common
	Oral sores[b]	Not known
Skin and subcutaneous tissue disorders	Pruritus[c]	Common
	Alopecia Rash[d]	Not known
Musculoskeletal and connective tissue disorders	Muscle spasms	Common
General disorders and administration site conditions	Injection site reactions[a]	Common

[a] See section "Description of selected adverse reactions"
[b] Oral sores includes preferred terms of stomatitis, mouth ulceration, oral mucosal blistering.
[c] Pruritus includes preferred terms of generalised pruritus, pruritus and pruritic rash.
[d] Rash includes preferred terms of rash papular, exfoliative rash, rash erythematous, urticaria, blister.

Description of selected adverse reactions

Injection site reactions
In the integrated 12-week placebo-controlled phase of the studies, injection site reactions were mild and mostly transient. There was one case of discontinuation in a patient receiving the 70 mg dose due to injection site rash. The most frequent injection site reactions were localised pain, erythema and pruritus. Injection site pain typically subsided within 1 hour after administration.

Cutaneous and hypersensitivity reactions
In the integrated 12-week placebo-controlled phase of the studies, non-serious cases of rash, pruritus and swelling/oedema were observed, which in the majority of cases were mild and did not lead to treatment discontinuation.

In the post-marketing setting, cases of anaphylaxis and angiodoema were observed.

Immunogenicity
During the double-blind treatment phase of the clinical studies, the incidence of anti-erenumab antibody development was 6.3% (56/884) among subjects receiving a 70 mg dose of erenumab (3 of whom had *in vitro* neutralising activity) and 2.6% (13/504) among subjects receiving the 140 mg dose of erenumab (none of whom had *in vitro* neutralising activity). In an open-label study with up to 256 weeks of treatment, the incidence of anti-erenumab antibody development was 11.0% (25/225) among patients who only received 70 mg or 140 mg of Aimovig throughout the entire study (2 of whom had *in vitro* neutralising activity). There was no impact of anti-erenumab antibody development on the efficacy or safety of erenumab.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported in clinical studies.

Doses up to 280 mg have been administered subcutaneously in clinical studies with no evidence of dose-limiting toxicity.

In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.