Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflets

Note:

This Summary of Product Characteristics and package leaflet is the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the newly agreed wording as provided below.

I. Summary of Product Characteristics

[...]

Section 4.1 Therapeutic indications

[The wording of this section should be read as below]

- Prophylactic treatment of severe intractable migraine (with or without aura) with functional disability in adults.

[*Invented name*] is to be used only following unsuccessful treatment with other standard classes of drugs (see section 4.4) after sufficient treatment duration (at least 4 months) at the maximal tolerated dose. Serious intolerance or contra-indication to a first line drug is regarded as treatment failure.
[*Invented name*] is not effective for treating a migraine attack that is already present.

- Prophylactic treatment of episodic and chronic cluster headache in adults.

Patients should have failed at least 2 classes of drugs before starting methysergide (see section 4.4). The minimal duration of treatment before concluding failure is 2 months.

Section 4.2 Posology and method of administration

[This section should be amended to reflect the following wording]

Methysergide treatment should be initiated and supervised by specialised physicians with experience in the treatment of migraine and cluster headache. (see section 4.4 regarding the need for specialist monitoring requirements)

Treatment must not begin until after the patient has been examined for any pre-existing fibrotic conditions. Once treatment is commenced the patient must be examined for occurrence of fibrosis at 6-monthly intervals, this examination should include a reassessment of the benefit: risk balance in the individual patient.

<u>Posology</u>

Adults

<u>Migraine prophylaxis</u>
The initial dose is one tablet (1-1.65 mg) per day at mealtime. The dosage may be gradually increased in divided daily dose until the optimal dose is reached. The maximum dose should not exceed 6 mg per day. The duration of continuous administration must not exceed six months. A treatment-free interval of at least 4 weeks must be allowed between courses.

<u>Cluster headaches</u>
For episodic cluster headache, the treatment duration should be adjusted according to the usual duration of the episodes, which would normally be no longer than 2 or 3 months. The maximum dose should not exceed 6 mg per day.
For chronic cluster headache, the therapeutic dose would normally be 6 mg but a higher dose may sometimes be required. The duration of continuous administration should not exceed six months. A treatment-free interval of at least 4 weeks must be allowed between courses.

Paediatric population

[*Invented name*] should not be used in the paediatric population.

[...]

Section 4.4 Special warnings and precautions for use

[This section should be amended to reflect the following wording]

Because of the potential serious safety concerns (in particular fibrotic reactions), methysergide should only be used after other treatment have failed.

- For prophylactic treatment of severe intractable migraine a number of other classes of treatment may be considered (e.g. beta-blockers, anticonvulsivants, calcium channel blocker or tricyclic antidepressants).

- For prophylactic treatment of episodic and chronic cluster headache at least two other classes of treatment should be considered first (e.g. verapamil, topiramate or lithium).

Patients should be informed on the risk of fibrosis with methysergide therapy and should accept the need for periodic investigations as described below.

The treatment should be stopped in patients who have not responded adequately in the first 2-3 months.

An initial screen must be performed prior to commencing methysergide therapy to exclude patients with pre-existent fibrosis or any other pathology that might put them at increased risk of developing fibrosis.

The following investigations should be performed prior to initiation of treatment with methysergide and at 6-monthly intervals thereafter: cardiac ultrasound, pulmonary function tests, abdominal MRI.

Patients should be examined regularly for the presence of: peripheral oedema, leg discolouration, digital clubbing, weak/irregular pulse(s), tachycardia, cardiac murmur, vascular bruits, raised jugular vein pressure, lung basal crepitations, pleural/pericardial friction rubs, abdominal/flank masses/tenderness.

During clinical assessment of the patient, particular attention should be paid to complaints of: abdominal, loin or chest pain, palpitations, dyspnoea, dry cough, nausea, malaise, fatigue, anorexia/weight loss, urinary symptoms, pain/coldness/numbness in limbs.

If symptoms suggestive of a fibrosis occur, treatment with methysergide should be discontinued unless an alternative aetiology is confirmed.

The duration of continuous administration must not exceed six months because of the risk of fibrosis (see section 4.8). A treatment-free interval of at least 4 weeks must be allowed between courses. The need to continue treatment should be re-assessed, and the optimal timing for reintroduction discussed with the patient.

It is recommended to taper the dosage gradually over the last two to three weeks of a course of treatment, so as to prevent a rebound effect on headaches.

<[*Invented name*] contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.>

<Or>

<[*Invented name*] contains lactose and sucrose. Patients with rare hereditary problems of galactose or fructose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.>

[…]

Section 4.8 Undesirable effects

[This section should be amended to reflect the following wording]

[…]

Nervous system disorders

Insomnia, drowsiness, dizziness, minor psychological changes of a temporary nature (nervousness, restlessness, depression and confusion in rare cases).

Cardiac and vascular disorders

There have been isolated reports of myocardial infarct, especially in patients who do not pay attention to the contraindications regarding coronary disorders or the use of vasoconstrictive medications.

Valvular fibrosis (see General disorders).

Edema and vasoconstriction of the large and small arteries can occur. Depending on the location of the affected blood vessel, this complication may be expressed as precordial (angina) or abdominal pain, as cold, dull, and painful sensations in the extremities, with or without paresthesia, as reduced or absence of a pulse, and theoretically, through arterial hypertension.

Respiratory, thoracic and mediastinal disorders

Pleuro-pulmonary fibrosis (see General disorders), dyspnoea, pleurisy, pleural effusion.

Gastrointestinal disorders

Nausea and vomiting may occur, but these undesirable effects are often less severe if [*Invented name*] is taken at mealtime.

Retro-peritoneal fibrosis (see General disorders).

Skin disorders

Skin reactions (e.g. rash, urticaria)

General disorders

Fibrotic reactions have been reported, especially of the pleura and retro-peritoneum, and also of the pericardium and cardiac valves. These reactions are potentially serious and occasionally life threatening. Retroperitoneal Fibrosis may occur. Although symptoms may sometimes improve after cessation of therapy in some cases, fibrotic reactions may also persist.

Pleuro-pulmonary fibrosis presents as precordial pains, dyspnoea, pleural frictional noise, lung basal crepitations or pleural effusion, digital clubbing, dry cough, anorexia and weight loss.

Retroperitoneal fibrosis may cause obstruction of the urinary tract with symptoms such as general asthenia, back pain, lumbar pain, dysuria, oliguria, raised blood nitrogen, nausea, anorexia, and vascular insufficiency, weak pulse and skin discolouration in the lower limbs.

Valvular fibrosis may cause changes in cardiac function. This may be observed as heart or vascular murmurs, tachycardia, peripheral oedema, raised JVP or palpitations.

The medication must be stopped as soon as one of these symptoms or signs has been established.

[…]

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.

II. Package Leaflet

[...]

1. What [*Invented name*] is and what it is used for

[The wording of this section should be read as below]

[*Invented name*] belong to a group of medicines called antimigraine drugs.

[*Invented name*] is taken by people who get severe migraines, with or without an aura, that affect their ability to go about their normal lives. It is taken regularly as a preventative measure to reduce how often they get the migraines. However, it should only be used after other standard treatments have failed, those treatments should have been tried for at least 4 months at the maximum dose without success before [*Invented name*] is started.

[*Invented name*] should not be used to stop a headache once it has started.

[*Invented name*] is also taken by people who have episodes or regular 'cluster' headaches. It is taken regularly as a preventative measure to reduce how often they get these headaches. However, it should only be used after at least two other types of medication for treating this type of headache have been tried for at least 2 months and failed to adequately treat the cluster headaches.

2. What you need to know before you take *[Invented name]*

[...]

Take special care with [*Invented name*]

[This section should be amended to reflect the following wording]

Before you take [*Invented name*] tell your doctor if:

You notice numbness or tingling in your fingers and toes.

Your doctor will perform some tests before the start of treatment and then every 6 months to ensure that you do not have or develop fibrosis (scarring within body organs). The tests will include a heart ultrasound, tests on how well your lungs are functioning and an abdominal scan such as a MRI.

If you notice any of the following symptoms you must immediately inform your doctor: pain in your chest or abdomen, awareness of your heart beat, difficulty in breathing, dry cough, nausea, general weakness, fatigue, loss of appetite/weight loss, urinary symptoms, pain/coldness/numbness in limbs. Your doctor will review and decide if you must stop the medication.

The treatment should be stopped in patients who have not responded adequately in the first 2-3 months.

You must not take methysergide continuously (without a break) for longer than six months. Speak to your doctor if this is the case. A treatment–free interval of at least 4 weeks must be allowed between courses. It is recommended to taper the dosage gradually over the last two to three weeks of a course of treatment, so as to prevent a rebound effect on headaches.

<Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take [*Invented name*].>

<Or>

<Patients with rare hereditary problems of galactose or fructose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take [*Invented name*].>

[…]

3. How to take [*Invented name*]

[This section should be amended to reflect the following wording]

You should only get your medication initiated and supervised by a doctor who specialises in the treatment of migraine and cluster headache (neurologist).

Always take [*Invented name*] exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

To start, take one tablet daily.
Then increase the dose gradually according to your doctor's instructions.

Migraine
Treatment duration should not exceed 6 months.

Cluster headache
For episodic cluster headaches, the duration of treatment will be adjusted according to the usual duration of the episodes but normally no longer than 2-3 months. For chronic cluster headaches, treatment duration should not exceed 6 months.

In between two treatments there should be an interval of 3-4 weeks in order to check whether you still need to take [*Invented name*]. Discontinuation of the treatment should be done gradually (in 2 or 3 weeks).

An abrupt cessation of treatment is necessary in the event of a fibrotic reaction.

[*Invented name*] should not be used in children.

Route and method of administration

Take the tablets during a meal with some drink.

[…]

4. Possible side effects

[This section should be amended to reflect the following wording]

Like all medicines, [*Invented name*] can cause side effects, although not everybody gets them.

Nervous system disorders

Insomnia, somnolence, dizziness, minor mood changes (nervousness, restlessness, depression and confusion in rare cases).

Cardiac and vascular disorders
There have been isolated reports of myocardial infarct, especially in patients who do not pay attention to the contraindications regarding coronary disorders or the use of vasoconstrictive medications.

Valvular fibrosis (see General disorders).

Edema and vasoconstriction of the large and small arteries can occur. Depending on the location of the affected blood vessel, this complication may be expressed as chest pain or abdominal pain, as cold, dull, and painful sensations in the extremities, with or without numbness, as reduced or absence of a pulse, and theoretically, through arterial tension increase.

Respiratory, thoracic and mediastinal disorders

Pleuro-pulmonary fibrosis (see General disorders), difficulty of breath, pleura inflammation, presence of fluid in the pleura.

Gastrointestinal disorders

Nausea and vomiting, particularly if [*Invented name*] is taken outside meals.
Retro-peritoneal fibrosis (see General disorders).

Skin disorders

Skin reactions (e.g. rash, urticaria).

General disorders

If [*Invented name*] is taken uninterruptedly for a long time, fibrosis (accumulation of scarring in the body organs) was seen at the pleural site (membrane covering the lungs), the peritoneum (membrane covering the abdominal cavity as well as the abdominal organs) and the heart valves.

Fibrotic symptoms of the pleura are: chest pain and shortness of breath, dry cough and weight loss.

Fibrosis of the retroperitoneum can cause symtpoms such general discomfort, back pain, waist- or rib pain, pain during urination, reduced urine production, loss of appetite and skin discolouration in the legs.

Heart valve fibrosis may cause increased heart rate, swelling in the hands and feet and can be identified by clinical examination.

The medication must be stopped as soon as one of these symptoms or signs has been established.

[...]

Reporting of side effects

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.