Annex I

List of the names, pharmaceutical form, strengths of the medicinal products, route of administration, marketing authorisation holders in the member states
<table>
<thead>
<tr>
<th>Member State (in EEA)</th>
<th>Marketing Authorisation Holder</th>
<th>Invented name</th>
<th>Strength</th>
<th>Pharmaceutical Form</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Amdipharm Ltd Temple Chambers 3 Burlington Road Dublin 4 Ireland</td>
<td>Deseril</td>
<td>1mg</td>
<td>Coated tablet</td>
<td>Oral use</td>
</tr>
<tr>
<td>France</td>
<td>Amdipharm Ltd Temple Chambers 3 Burlington Road Dublin 4 Ireland</td>
<td>DESERNIL</td>
<td>1,65mg</td>
<td>Tablet</td>
<td>Oral use</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Amdipharm Ltd Temple Chambers 3 Burlington Road Dublin 4 Ireland</td>
<td>Deseril</td>
<td>1mg</td>
<td>Tablet</td>
<td>Oral use</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Alliance Pharmaceuticals Ltd Avonbridge House 2 Bath Road, Chippenham Wiltshire, SN15 2BB United Kingdom</td>
<td>Deseril Tablets 1mg</td>
<td>1mg</td>
<td>Tablet</td>
<td>Oral use</td>
</tr>
</tbody>
</table>
Annex II

Scientific conclusions and grounds for the variation of the marketing authorisations
Scientific conclusions

Overall summary of the scientific evaluation of methysergide containing medicinal products (see Annex I)

Methysergide is an ergot alkaloid, first described in clinical practice in 1959. Methysergide binds with varying affinities to a range of serotonergic receptors (5-HT receptors). In particular, it binds to and is an antagonist of the 5HT2B receptor. There are a number of pharmacological pathways by which methysergide may be effective in preventing migraine, for instance some data support the role of antagonism of the 5-HT2B receptor in the prophylaxis of migraine.

Methysergide is currently indicated in the prophylaxis of migraine headache, cluster headache and also in the treatment of diarrhoea caused by carcinoid disease (specific wording of the indication may vary from product to product).

Methysergide containing products are currently authorised in the following EU countries: Belgium, France, the Netherlands and the United Kingdom.

In 2011, a French national pharmacovigilance review reported serious cases of valvulopathy, pulmonary, pleural and retroperitoneal fibrosis associated with methysergide containing medicinal products. Based on this, France considered that the benefit risk balance of methysergide containing products should be reviewed and triggered a referral under Article 31 of Directive 2001/83/EC.

Efficacy

The CHMP has considered the totality of the available data on the safety and efficacy of methysergide. For the indication “prophylaxis of migraine”, data were submitted from randomised, double-blind, placebo-controlled studies1,2,3,4. The results of these studies are suggestive of the efficacy of methysergide compared to placebo in the prophylaxis of migraine. In addition, further trials comparing methysergide with placebo or comparators were also presented, some of which also showed efficacy of methysergide compared to placebo in this indication5,6,7. The CHMP highlighted that these results should be taken with caution as these studies are old and generally not carried out with the current up-to-date methodology8.

The CHMP also noted that methysergide is included in the latest recommendations of migraine preventive treatments of the European Federation of Neurological Societies (EFNS; 2009)9 as drug of third choice for migraine prophylaxis for short-term use only, and in the latest French recommendations of 2013 as Grade B or C (probably effective) for migraine prophylaxis10. Considering the overall data available, the CHMP is of the opinion that there is some evidence of clinically significant efficacy of methysergide in the prophylactic treatment of severe and debilitating migraine.

4 Shekelle RB, Ostfeld AM. Methysergide in the migraine syndrome. Clin Pharmacol Ther 19645:201-204
With regard to the indication “cluster headache”, the applicant referred to a review\textsuperscript{11} which suggested the prophylactic efficacy of methysergide, particularly for the episodic form of cluster headache and to a study\textsuperscript{12} where 69% of cluster headache patients reported to have good to excellent results. Two studies, one observational and one prospective, reported less convincing evidence\textsuperscript{13} where around 26% patients had satisfactory, good or excellent outcomes. In a more recent review\textsuperscript{14}, methysergide and verapamil were cited as the most useful treatments of the episodic form of cluster headache. The CHMP noted that the clinical trial evidence for the efficacy of methysergide as a prophylactic treatment for cluster headache is less robust compared to the evidence for migraine prophylaxis and that the majority of studies have a number of limitations.

The CHMP further noted that methysergide is included as second choice treatment in the latest recommendations of cluster headache preventive treatments of the EFNS (2006)\textsuperscript{15} and is also included in the list of preventive therapies for cluster headache in recently published guidelines\textsuperscript{16,17,18}. In addition, the CHMP noted that methysergide is recommended by experts as a rescue treatment, reserved for patients in whom other treatments have failed.

No data was submitted in support of efficacy of methysergide in the “treatment of diarrhoea caused by carcinoid disease”, and it is therefore considered that efficacy in this indication has not been demonstrated. In this respect, the CHMP took note of the fact that one of the marketing authorisation holders of the products for which this indication is approved informed the CHMP of their intention to voluntarily withdraw the indication "diarrhoea caused by carcinoid syndrome".

The CHMP acknowledged the advice of the Scientific Advisory Group (SAG) which was convened in September 2013 during which the experts discussed, based on their clinical experience, whether it is possible to define a population for which there is a therapeutic need for oral methysergide-containing products when standard treatment for these indications have been ineffective. Based on the clinical experience of headache experts, the SAG considered that there is a small proportion of the populations suffering from migraine and from cluster headache that seems to benefit from treatment with methysergide, when previous treatments have failed.

The CHMP further took note of third party interventions received from patients and healthcare professionals during the assessment, highlighting the importance of maintaining availability of this product to a population that, albeit small, has few or no therapeutic alternatives for a debilitating condition.

Safety

In order to evaluate the safety of methysergide, the CHMP considered data from literature and safety database including spontaneous and literature reports.

The incidence rates of valvar and pulmonary fibrosis in patients treated with methysergide was shown to be similar to those of the general population\textsuperscript{19,20,21,22}. However, these results should be taken

\textsuperscript{16} MacGregor EA, Steiner TJ, Davies PGT. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache. British Association for the Study of Headache 2010(3rd edition (1st revision)).
\textsuperscript{19} Bana DS, MacNeal PS, LeCompte PM. Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. Am Heart J 1974;88(5):640-55.
with caution as methods of detection of fibrosis used in these studies are not sensitive enough, in particular for valvular fibrosis. The real incidence rate might be under-estimated and the risk of fibrosis is probably higher. Regarding the risk of retroperitoneal fibrosis, there is evidence of increased risk in patients treated with methysergide (200 versus 1.3 per 100 000 patients)\textsuperscript{23,24}.

Existing data seems to show that fibrosis development is not related to patient age. In addition, development of fibrosis appears to be correlated to treatment duration, as most patients developed fibrotic events after long-term therapy (at least one year). However, cases have also been reported with treatment duration up to six months, so occurrence of fibrosis with short-term treatment cannot be excluded. The majority of patients (92.4%) who developed fibrosis received daily doses of methysergide within the currently recommended (≤ 6 mg/day).

Taking into account the number of fibrosis cases reported and the probable under reporting, the risk of fibrotic reactions associated with methysergide cannot be excluded. The CHMP noted that fibrosis can be a life-threatening event and that some of the retroperitoneal fibrotic reactions reported are very severe (ureter fibrosis, bilateral uretic stenting, bilateral nephrostomy etc.).

The CHMP noted that the mechanistic basis for the fibrosis appears to be well-founded, and fits with the known association between methysergide use and fibrosis, which has been reported with respect of valvular heart disease since the mid-1960s. Since fibrotic reactions are believed to be associated with persistent agonist activation of the 5-HT\textsubscript{2B} receptor, long-term treatment with methysergide will expose patients to the potential for tissue fibrosis mediated by its principal active metabolite, methylergometrine. Therefore, the potential causal association between fibrotic reactions and methysergide cannot be excluded.

The CHMP considered the view of the SAG which recommended some measures to be taken in order to minimise the risk of fibrotic reactions when prescribing methysergide. These included restricted duration of treatment, optimal dose of treatment, specialist supervision and information for prescribing physicians and patients’ organisation. The SAG also considered that patients should be monitored at baseline and every six months while on treatment (heart ultrasound, abdominal magnetic resonance imaging (MRI), pulmonary function tests) in order to be able to identify all fibrosis before severe and potentially irreversible reactions have occurred.

Overall, the CHMP considered that methysergide seems to benefit a small patient population of migraine and cluster headache patients. However, in view of the demonstrated risk of fibrosis, adequate risk minimisation measures should be put in place. The indication should be restricted to patients with functional disability in whom other treatments have failed. The CHMP also recommended that methysergide treatment should be initiated and supervised by specialised physicians with experience in the treatment of migraine and cluster headache. Warnings on the risk of fibrosis should be included in the product information, alongside measures to monitor patients for development of fibrosis, and these should also be communicated to prescribers and patients using educational material.

**Benefit-risk balance**

Having considered the overall data provided by the MAH in writing, the CHMP concluded that the benefit-risk balance of methysergide is favourable in:


• the prophylactic treatment of severe intractable migraine (with or without aura) with functional disability in adults.

Methysergide is to be used only following unsuccessful treatment with other standard classes of drugs 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. Methysergide is not effective for treating a migraine attack that is already present.

• the prophylactic treatment of episodic and chronic cluster headache in adults. Patients should have failed at least 2 classes of drugs before starting methysergide. The minimal duration of treatment before concluding failure is 2 months.

This is subject to the agreed warnings, other changes to the product information and additional risk minimisation measures.

Regarding the indication “treatment of diarrhoea caused by carcinoid disease”, the CHMP concluded that the benefit-risk balance is negative as there is a clearly demonstrated risk of fibrosis but no evidence of benefit.
Grounds for variation to the terms of the marketing authorisations

Whereas

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for methysergide containing medicinal products.
- The Committee reviewed all available data on the efficacy and safety of methysergide containing medicinal products, in particular with regard to the risk of fibrotic reactions.
- The Committee considered that a causal association between methysergide and fibrotic reactions is likely based on available data (mainly relating to retroperitoneal fibrosis). Such adverse effects may be serious and in some cases irreversible and potentially fatal.
- The Committee noted that there is no evidence of efficacy of methysergide in the treatment of diarrhoea caused by carcinoid disease, and therefore the potential benefit for patients in this indication is outweighed by the identified risk.
- The Committee considered that there is some evidence for clinically significant efficacy of methysergide in the prophylactic treatment of severe, debilitating migraine and cluster headache for which therapeutic alternatives are limited. In addition, risk minimisation measures can be put in place to minimise the risk of fibrosis.
- Therefore the CHMP was of the opinion that the benefit-risk balance of methysergide containing products:
  - Is favourable for the prophylactic treatment of severe intractable migraine (with or without aura) with functional disability in adults. Methysergide is to be used only following unsuccessful treatment with other standard classes of drugs 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. Methysergide is not effective for treating a migraine attack that is already present. This is provided that the recommended risk minimisation measures are implemented;
  - Is favourable for the prophylactic treatment of episodic and chronic cluster headache in adults. Patients should have failed at least 2 classes of drugs before starting methysergide. The minimal duration of treatment before concluding failure is 2 months. This is provided that the recommended risk minimisation measures are implemented;
  - Is not favourable for the treatment of diarrhoea caused by carcinoid disease.

Therefore, in accordance with Article 116 of Directive 2001/83/EC, the CHMP recommends the variation to the terms of the marketing authorisation for methysergide containing medicinal products referred to in Annex I.
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.

Posology

Adults

Migraine prophylaxis
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.

Cluster headaches
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.

[...]

12
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 symptoms 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, 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.