ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES (EU/EEA)

Member State (EU/EEA)	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration
Czech Republic	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm, Germany	Valproat-Ratiopharm Chrono 300 mg	300 mg	Prolonged-release tablet	Oral use
Czech Republic	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm, Germany	Valproat-Ratiopharm Chrono 500 mg	500 mg	Prolonged-release tablet	Oral use
Germany	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm, Germany	Valproinsäure-ratiopharm chrono 300 mg Retardtabletten	300 mg	Prolonged-release tablet	Oral use
Germany	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm, Germany	Valproinsäure-ratiopharm chrono 500 mg Retardtabletten	500 mg	Prolonged-release tablet	Oral use
Italy	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm, Germany	Acido valproico E sodio Valproato Ratiopharm	300 mg	Prolonged-release tablet	Oral use
Italy	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm, Germany	Acido valproico E sodio Valproato Ratiopharm	500 mg	Prolonged-release tablet	Oral use
Luxembourg	Ratiopharm GmbH Postfach 3380 89070 Ulm, Germany	Valproinsäure Ratiopharm Chrono	300 mg	Prolonged-release tablet	Oral use
Luxembourg	Ratiopharm GmbH Postfach 3380 89070 Ulm Germany	Valproinsäure Ratiopharm Chrono	500 mg	Prolonged-release tablet	Oral use

Member State (EU/EEA)	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration
The Netherlands	Ratiopharm Nederland B.V. Florapark 4 2012HK Haarlem The Netherlands	Natriumvalproaat ratiopharm chrono 300 mg	300 mg	Prolonged-release tablet	Oral use
The Netherlands	Ratiopharm Nederland B.V. Florapark 4 2012HK Haarlem The Netherlands	Natriumvalproaat ratiopharm chrono 500 mg	500 mg	Prolonged-release tablet	Oral use
Poland	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Valpro-ratiopharm Chrono 300 mg	199,8 mg + 87 mg	Prolonged-release tablet	Oral use
Poland	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Valpro-ratiopharm Chrono 500 mg	333 mg + 145 mg	Prolonged-release tablet	Oral use
Portugal	Ratiopharm – Comércio e Indústria de Produtos Farmacêuticos, Lda. Rua Quinta do Pinheiro – Edifício Tejo 6° Piso Carnaxide P-2790-143	Ácido Valpróico Ratiopharm 300 mg Comprimidos de libertação prolongada	300 mg	Prolonged-release tablet	Oral use
Portugal	Ratiopharm – Comércio e Indústria de Produtos Farmacêuticos, Lda. Rua Quinta do Pinheiro – Edifício Tejo 6° Piso Carnaxide P-2790-143 Portugal	Ácido Valpróico Ratiopharm 500 mg Comprimidos de libertação prolongada	500 mg	Prolonged-release tablet	Oral use
Slovakia	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm	Valpro ratiopharm Chrono	500 mg	Prolonged-release tablet	Oral use

Member State (EU/EEA)	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration
	Germany				
United Kingdom	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Valprotek CR 300 mg (prolonged release) tablets	300 mg	Prolonged-release tablet	Oral use
United Kingdom	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Valprotek CR 500 mg (prolonged release) tablets	500 mg	Prolonged-release tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF VALPROATE-RATIOPHARM CHRONO 300/500 MG RETARDTABLETTEN AND ASSOCIATED NAMES (see Annex I)

Bipolar disorder is a severe mental disorder characterized by recurrent episodes of mania and depression, which as a recurrent affective illness produces significant distress and dysfunction, ranking among the top 30 causes of worldwide disability.

The treatment of bipolar disorder includes management of the current mood episode and prevention of recurrence of next mood episodes. Although the pathogenesis of bipolar disorder is unclear, it is known that mood stabilizers, such as valproate, can prevent its recurrence.

Among the mood stabilizers lithium has the longest track record and is therefore a reasonable first choice. However, it has recently been estimated that up to 40% of the patients with bipolar disorder do not or insufficiently respond to an adequate lithium therapy. In addition there is a considerable risk due to the narrow therapeutic window of this substance. Anticonvulsants are increasingly becoming an alternative.

Valproate is a well-known anti-epileptic substance. In most of the EU Member States valproate is also approved (as valproic acid, sodium valproate, valproate semisodium) for the treatment of patients with bipolar disorder (approved in 25 European countries, in 21 countries with a first-line indication).

Concerns were raised by the Netherlands regarding the efficacious and safe use of Valproate-ratiopharm chrono 300/500 mg Retardtabletten (and associated names) in the acute treatment of manic episodes and the prevention of recurrence of mood episodes in patients with bipolar disorder. It was highlighted that although the indication exists in many Member States, sustained efficacy both in acute mania as well as in the prevention of recurrence of mood episodes has not been clearly demonstrated in well designed clinical trials which comply with the requirements of the CPMP Note for Guidance on Clinical Investigation of Medicinal products for the Treatment and Prevention of Bipolar Disorder (CPMP/EWP/567/98).

1. Efficacy

1.1 *Mania*

To support the bipolar indication the MAHs submitted several published studies. The evidence of the efficacy of valproate in the treatment of bipolar disorder comes from sixteen randomised, comparative double-blind or open-label clinical trials.

These studies included nearly 2,500 patients, of whom over 1,400 received valproate. As such, this represents one of the largest bodies of clinical trial data relating to the pharmacotherapy of bipolar disorder. In addition, valproate has been used as the reference comparator treatment in many Phase III studies of atypical antipsychotic drugs in the treatment and prevention of mania.

Based on the literature references provided it can be concluded that there is evidence for the efficacy of valproate in the acute treatment of manic episode, which has been demonstrated in placebo controlled studies of three weeks. There is also some evidence for maintenance of effect in treatment of acute mania episode (up to 12 weeks), although the 12 weeks studies lack a placebo arm, which is a deficiency. In other words, the conducted studies demonstrate efficacy of valproate in the treatment of acute mania over 21 days, but evidence for the maintenance of the treatment effect up to 12 weeks of treatment is not considered complete.

According to the CHMP recommendation for Valproate-ratiopharm chrono 300/500 mg Retardtabletten and associated names the indication should be adapted in the following due to the limitations and shortcomings of the data from clinical trials:

> "*Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate for acute mania*."

There is a positive benefit-risk relation with regard to the aforementioned indication.

1.2 *Prevention of Recurrence of mood episodes*

Concerning recurrence prevention of mood episodes, evidence of efficacy of valproate is mainly based on two double-blind studies with a maintenance period of 52 weeks and 20 months duration, respectively (Bowden *et al.,* 2000 and Calabrese *et al*., 2005).

Whereas the Bowden study which was lithium- and placebo- controlled failed to show a statistically significant difference with respect to the primary outcome criterion (time to recurrence of any mood episode), patients treated with valproate had better outcomes on several secondary outcome measures than those treated with lithium or placebo. After 12 months of treatment following a manic index episode, 41% of patients treated with valproate were still in remission compared to 24% of patients in the lithium group and 13% of patients in the placebo group. *Post-hoc* analyses were done of the large Bowden study. Whereas, in the original analysis time to recurrence of any mood episode or depressive episode, respectively was not significantly different in the three treatment groups, *post-hoc* analyses showed that valproate treated patients dropped out significantly less frequent than placebo treated patients because of a mood episode and due to a depressive episode, respectively, whereas the respective difference was not statistically significant compared to lithium treated patients.

In the two-arm study performed by Calabrese and co-workers (2005) patients in the valproate group performed better in several efficacy parameters compared to the lithium group (in a statistically non-significant way), however significantly more patients in the lithium group experienced various adverse effects (tremor, polyuria, polydipsia) compared to the valproate group. It could be critisised that the latter study was not placebo-controlled; however the use of lithium in bipolar disorder, especially in the recurrence prevention is the established standard of care.

As conclusion the recurrence prevention of both mania and depression has not been demonstrated. The two recurrence prevention studies are of sufficient duration and have an active comparator as requested by European guidelines. However one study is lacking a short placebo arm, which is a deficiency and brings doubts about the validity of the results. In addition the time to recurrence of manic and depression events has not shown differences. Evidence of efficacy of valproate in the prevention of mood episodes is thus not completely convincing based on the performed clinical studies alone.

1.3 *Chemical forms and formulations of valproate*

Based on the submitted data it cannot be concluded, that efficacy of valproate in the claimed indication is dependent on chemical form or formulation. Furthermore, according to clinical practice and the dose recommendations, the daily dose should be adapted individually to the clinical response between a specific dose range and the lowest effective dose should be used in the prevention of recurrence in bipolar disorder. However, for theoretical reasons slow-release formulations could be advantageous for compliance reasons and also for avoiding high plasma peaks which may be accompanied by frequent adverse effects. Therefore the CHMP recommended that valproate in the indication treatment of acute episodes is restricted to modified-release (solid oral) formulations.

2 Safety

The available studies on the use of valproate to treat patients with bipolar disorder have shown that the drug was generally well tolerated and revealed no unexpected safety concern. The safety profile of valproate is well characterised from forty years of experience in the treatment of epilepsy. The major potentially serious safety concerns relate to liver dysfunction and pancreatitis. No unexpected signals have been identified from post-marketing surveillance. Dedicated studies have shown that valproate can be used safely in combination with antipsychotic drugs. Moreover, no specific safety issues have been identified in studies in which antidepressant co-medication has been used in patients with bipolar disease.

Adverse Events

Following the literature presented as well the post-marketing experience the adverse events of "nausea", "sedation" and "extrapyrimidal disorders" are proposed to be added to the Section 4.8 "Undesirable effects" of the SPC. The MAHs should look into their respective safety databases and add the appropriate frequency of occurrence to the above additional adverse events.

Chemical forms and formulations of valproate

With respect to the formulation, there is some evidence that gastro-resistant tablets might provide some advantages in terms of safety as compared to immediate release formulation.

Pregnancy

A teratogenic risk associated with the use of valproate in pregnant women, including the potential for delayed intellectual development has been identified following in utero exposure to valproate. Therefore, in women envisaging a pregnancy, valproate should not be used for the treatment of manic episodes, unless safer alternatives prove to be ineffective or are not tolerated. Women of child-bearing potential have to use effective contraception.

Suicidality

In 2008, in light of the results of the US FDA meta-analysis of clinical trial data for antiepileptics, and in light of the spontaneous and literature reports, the PhVWP concluded that any antiepileptic drug may be associated with a low risk of suicidal thoughts and behaviour. On the basis of the evidence available to the PhVWP, it was agreed that SPCs for all antiepileptics across the European Union should be modified with regard to suicidality with the addition of a warning

2.2 *Risk Management Plan*

The need for a Risk Management Plan was discussed with the MAHs. Taking into account that in different EU member States the authorised valproate products may have or not the indication for the bipolar disorder the CHMP has the following proposal:

The MAHs for valproate authorised products who apply for the new indication should contact the national competent authorities (NCAs) of the respective member states in order to submit a Risk Management Plan. The content, objectives and implementation of the RMP should be discussed between the relevant MAH and the NCA and it should be agreed and implemented.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas

- The Committee considered the referral made under article of Article 6 of Commission Regulation (EC) No 1084/2003, for Valproate-ratiopharm chrono 300/500 mg Retardtabletten (and associated names) initiated by The Netherlands.

- The Committee considered all the available data submitted on efficacy and the safety for Valproate-ratiopharm chrono 300/500 mg Retardtabletten (and associated names), in relation to the treatment of mania in bipolar disorder as well in the prevention of recurrence of mood episodes.

- The Committee concluded that Valproate-ratiopharm chrono 300/500 mg Retardtabletten (and associated names) have a positive benefit-risk ratio in the proposed amended indication for the treatment of mania in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to the medicinal product for acute mania.

- The Committee concluded that the Product Information of all Valproate-ratiopharm chrono 300/500 mg Retardtabletten (and associated names) should include information to the amended indication on the treatment of mania in bipolar disorder when lithium is contraindicated or not tolerated and therefore recommended the amendments to the relevant sections of the Summary of Product Characteristic and Package Leaflet accordingly.

  Furthermore, when the proposed indication is granted the MAHs should submit a Risk Management Plan to the NCAs for assessment.

As a consequence, the CHMP has recommended the maintenance of the Marketing Authorisations for the medicinal products referred to in Annex I for which the amendments to the relevant sections of the Summary of Product Characteristics and Package Leaflet are set out in Annex III and in accordance to the conditions set out in Annex IV.

As a consequence,the CHMP has recommended the granting of the variation for which the Summary of Product Characteristics and Package Leaflet is set out in Annex III for Valproate-ratiopharm chrono 300/500 mg Retardtabletten and associated names (see Annex I).

ANNEX III

AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND THE PACKAGE LEAFLET

Note: These amendments to the summary of product characteristics and package leaflet are valid at the time of the Commission Decision.
After the Commission Decision the National Competent Authorities will update the product information as required.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR VALPROATE-RATIOPHARM CHRONO 300/500 MG RETARDTABLETTEN AND ASSOCIATED NAMES

4.1 Therapeutic indications

[…]

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to <valproate> for acute mania.
[…]

4.2 Posology and method of administration

Manic episodes in bipolar disorder:

In adults:
The daily dosage should be established and controlled individually by the treating physician.
The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg <valproate>/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient.
The mean daily dose usually ranges between 1000 and 2000 mg <valproate>. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.
Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

In children and adolescents:
The safety and efficacy of {invented name} for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

[…]

Method and duration of administration:

The prolonged-release tablets should preferably be taken 1 hour before meals (on an empty stomach in the morning). In case of gastrointestinal side-effects due to treatment, the prolonged-release tablets should be taken during or after a meal. They should be swallowed whole or in halves, not chewed, and taken with plenty of fluid (e.g. a glass of water).

The duration of treatment is determined by the treating doctor.

Seizures:
Antiepileptic therapy is always a long-term therapy.
A specialist doctor (neurologist, neuropaediatrician) should decide upon dose titration, the duration of treatment and withdrawal of *Valproinsäure-ratiopharm chrono* on an individual basis. Generally, in the treatment of seizures no dose reduction or withdrawal of the medicine should be attempted until the patient has been free of seizures for at least two to three years. Withdrawal must take the form of a gradual dose reduction over a period of one to two years. Children may be allowed to grow out of the dose per kg body weight instead of making age-related dose adjustments, whereby EEG findings should not deteriorate.

Experience with long-term use of *Valproinsäure-ratiopharm chrono* is limited, particularly in children under 6 years of age.

[…]

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for <active substance>. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
[…]

4.6 Pregnancy and lactation

Manic episodes in bipolar disorder:
This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of child-bearing potential have to use effective contraception during treatment.

4.8 Undesirable effects

Nausea, sedation, extrapyramidal disorders.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF PACKAGE LEAFLET FOR VALPROATE-RATIOPHARM CHRONO 300/500 MG RETARDTABLETTEN AND ASSOCIATED NAMES

1. WHAT {INVENTED NAME} IS AND WHAT IT IS USED FOR

{Invented name} is a medicine for the treatment of […] and mania.

{Invented name} is used in the treatment of

[…]

~~- acute mania and for the prevention of recurrence in patients with bipolar disorder~~
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder". {Invented name} can be used when lithium can not be used.

2. BEFORE YOU TAKE {INVENTED NAME}

Take special care with {INVENTED NAME}
A small number of people being treated with anti-epileptics such as <active substance> have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Children and adolescents
Children and adolescents under 18 years of age:
{Invented name} should not be used in children and adolescents under 18 years of age for the treatment of mania.

Pregnancy and breast-feeding

Pregnancy

Manic episodes in bipolar disorder
You should not take this medicine if you are pregnant or a women of child-bearing age unless explicitly advised by your doctor. If you are a woman of child-bearing age, you have to use effective contraception during treatment.

Breast feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Valproic acid passes into the breast milk. As only very small amounts are found, however, these do not generally present any risk to the child and weaning is not usually necessary.

3. HOW TO TAKE {INVENTED NAME}

Mania
The daily dosage should be established and controlled individually by your doctor. ~~The daily dose will be determined according to age and body weight.~~

Initial dose
The recommended initial daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg sodium valproate/kg body weight has also shown an acceptable safety profile. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect.

Mean daily dose
The recommended daily doses usually range between 1000 mg and 2000 mg.

<Valproinsäure-ratiopharm chrono 300 Retardtabletten>
The recommended daily doses usually range between 1000 mg and 2000 mg (3 ½ and 6 ½ tablets). The daily dose should be adapted ~~individually~~ to the clinical response to establish the lowest effective dose for ~~of~~ the individual patient.

<Valproinsäure-ratiopharm chrono 500 Retardtabletten>
The recommended daily doses usually range between 1000 mg and 2000 mg (2 and 4 tablets). The daily dose should be adapted ~~individually~~ to the clinical response to establish the lowest effective dose for ~~of~~ the individual patient.

~~Preventive treatment of mania will be adapted individually using the lowest effective dose.~~
~~Your doctor will determine the exact dose required on an individual basis.~~
~~Please follow his/her instructions, otherwise you will not fully benefit from your medicine.~~

Children and adolescents under 18 years of age:
[…] should not be used in children and adolescents under 18 years of age for the treatment of mania.

4. POSSIBLE SIDE EFFECTS

Nausea, sedation, extrapyramidal disorders.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF PACKAGE LEAFLET FOR VALPROATE-RATIOPHARM CHRONO 300/500 MG RETARDTABLETTEN AND ASSOCIATED NAMES

1. WHAT {INVENTED NAME} IS AND WHAT IT IS USED FOR

{Invented name} is a medicine for the treatment of […] and mania.

{Invented name} is used in the treatment of

[…]

~~- acute mania and for the prevention of recurrence in patients with bipolar disorder~~
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder". {Invented name} can be used when lithium can not be used.

2. BEFORE YOU TAKE {INVENTED NAME}

Take special care with {INVENTED NAME}
A small number of people being treated with anti-epileptics such as <active substance> have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Children and adolescents
Children and adolescents under 18 years of age:
{Invented name} should not be used in children and adolescents under 18 years of age for the treatment of mania.

Pregnancy and breast-feeding

Pregnancy

Manic episodes in bipolar disorder
You should not take this medicine if you are pregnant or a women of child-bearing age unless explicitly advised by your doctor. If you are a woman of child-bearing age, you have to use effective contraception during treatment.

Breast feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Valproic acid passes into the breast milk. As only very small amounts are found, however, these do not generally present any risk to the child and weaning is not usually necessary.

3. HOW TO TAKE {INVENTED NAME}

Mania
The daily dosage should be established and controlled individually by your doctor.~~ The daily dose will be determined according to age and body weight.~~

If you take {invented name} for the treatment of mania, your doctor may possibly consider to discontinue the treatment.

Initial dose

The recommended initial daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg sodium valproate/kg body weight has also shown an acceptable safety profile. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect.

Mean daily dose
The recommended daily doses usually range between 1000 mg and 2000 mg.

<Valproinsäure-ratiopharm chrono 300 Retardtabletten>
The recommended daily doses usually range between 1000 mg and 2000 mg (3 ½ and 6 ½ tablets). The daily dose should be adapted ~~individually~~ to the clinical response to establish the lowest effective dose for ~~of~~ the individual patient.

<Valproinsäure-ratiopharm chrono 500 Retardtabletten>
The recommended daily doses usually range between 1000 mg and 2000 mg (2 and 4 tablets). The daily dose should be adapted ~~individually~~ to the clinical response to establish the lowest effective dose for ~~of~~ the individual patient.

~~Preventive treatment of mania will be adapted individually using the lowest effective dose.~~
~~Your doctor will determine the exact dose required on an individual basis.~~
~~Please follow his/her instructions, otherwise you will not fully benefit from your medicine.~~

Children and adolescents under 18 years of age:
/…/ should not be used in children and adolescents under 18 years of age for the treatment of mania.

4. POSSIBLE SIDE EFFECTS

Nausea, sedation, extrapyramidal disorders.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

CONDITIONS OF THE MARKETING AUTHORISATIONS

National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

Summary of Product Characteristics and Package Leaflet.

The MAHs should update the Product Information to include the relevant sections as proposed by the CHMP regarding the proposed amended indication for the treatment of mania in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to the medicinal product for acute mania.

Risk Management Plan

Following the European Commission Decision the Risk Management Plan should be submitted with any new application for extending the indication regarding the treatment of mania in bipolar disorder.