ANNEX I

LIST OF THE INVENTED NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES (EEA)

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Dermapharm GmbH Türkenstraße 25/12 A-1090 Wien Austria	Parfenac - Creme	50 mg/g	Cream	Cutaneous use
Austria	Dermapharm GmbH Türkenstraße 25/12 A-1090 Wien Austria	Parfenac - dermatologische Emulsion	50 mg/g	Cutaneous emulsion	Cutaneous use
Austria	Dermapharm GmbH Türkenstraße 25/12 A-1090 Wien Austria	Parfenac - Fettsalbe	50 mg/g	Ointment	Cutaneous use
Austria	Dermapharm GmbH Türkenstraße 25/12 A-1090 Wien Austria	Parfenac - Salbe	50 mg/g	Ointment	Cutaneous use
Bulgaria	Stada Arzneimittel AG, Stadastrasse 2-18 61118 Bad Vilbel Germany	Mastu S Forte	Bufexamac 250 mg, Bismuth subgallate 100 mg, Titanium dioxide 100 mg, Lidocaine hydrochloride 10 mg	Suppositories	Rectal use
Bulgaria	Stada Arzneimittel AG Stadastrasse 2-1 861118 Bad Vilbel Germany	Mastu S	Bufexamac 50 mg/g, Bismuth subgallate 50 mg/g, Titanium dioxide 50 mg/g, Lidocaine hydrochloride 5mg/g	Rectal ointment	Rectal use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Czech Republic	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	MASTU S FORTE	Bufexamac 250 mg, Bismuth subgallate 100 mg, Titanium dioxide 100 mg, Lidocaine hydrochloride 10 mg	suppository	Rectal use
Czech Republic	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	MASTU S	Bufexamac 50 mg/g, Bismuth subgallate 50 mg/g, Titanium dioxide 50 mg/g, Lidocaine hydrochloride 5 mg/g	rectal ointment	Rectal use
France	Pierre Fabre Medicament 45 place Abel Gance 92654 Boulogne cedex France	BUFAL 5 POUR CENT, crème en tube	5 g/100 g	cream	Cutaneous use
France	Coopération Pharmaceutique Française Place Lucien Auvert 77020 Melun cedex France	BUFEXAMAC COOPER 5 pour cent, crème	5 g/100 g	cream	Cutaneous use
France	Wyeth Pharmaceuticals France Cœur Défense Tour A la Défanse 4 92931 Paris La Défense Cedex France	BUFEXAMAC NOVALIS 5 pour cent, crème	5 g/100 g	cream	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France	Wyeth Pharmaceuticals France Cœur Défense Tour A la Défanse 4 92931 Paris La Défense Cedex France	CALMADERM, crème pour application cutannée	5 g/100 g	cream	Cutaneous use
France	Wyeth Pharmaceuticals France Cœur Défense Tour A la Défanse 4 92931 Paris La Défense Cedex France	PARFENAC 5 POUR CENT, crème	5 g/100 g	cream	Cutaneous use
France	Wyeth Pharmaceuticals France Cœur Défense Tour A la Défanse 4 92931 Paris La Défense Cedex France	PARFENOIDE, crème pour application locale	5 g/100 g	cream	Cutaneous use
Hungary	Stada Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Mastu S	50mg Bufexamac (+5mg Lidocaine)/ 1g	ointment	Cutaneous use
Hungary	Stada Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Mastu S Forte	250mg Bufexamac, +10mg Lidocaine	suppository	Rectal use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Farmigea spa Via Giovan Battista Oliva 6/8 56121 PISA Italy	FANSAMAC	5 g/100 g	cream	Cutaneous use
Latvia	Stada Arzneimittel AG, Stadastraße 2-18 61118 Bad Vilbel Germany	Mastu S ointment	Bismuthi subgallas 50 mg, Bufexamacum 50 mg, Titanii dioxidum 50 mg Lidocaini hydrochloridum 5 mg/g	Ointment	Rectal use and Cutaneous use
Latvia	Stada Arzneimittel AG Stadastraße 2-18 61118 Bad Vilbel, Germany	Mastu S forte suppositories	Titanii dioxidum 250 mg, Lidocaini hydrochloridum100 mg, Bismuthi subgallas 100 mg, Bufexamacum 10 mg	Suppositories	Rectal use
Lithuania	Stada Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Mastu S	Bufexamac 50 mg/g, Bismuth subgallate 50 mg/g, Titanium dioxide 50 mg/g, Lidocaine hydrochloride monohydrate5 mg/g	Ointment	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Lithuania	Stada Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Mastu S forte	Bufexamac 250 mg, Bismuth subgallate 100 mg, Titanium dioxide 100 mg, Lidocaine hydrochloride monohydrate10 mg	Suppository	Rectal use
Luxembourg	PF MEDICAMENT 45, Place Abel Gance 92654 Boulogne Cedex France	BUFAL	5g/100g	cream	Cutaneous use
Portugal	Home Products de Portugal, Lda. Rua Dr. António Loureiro Borges 2 - Arquiparque - Miraflores 1495-131 Algés Portugal	Parfenac	50mg/g	Ointment	Cutaneous use
Romania	STADA ARZNEIMITTEL AG Stadastrasse 2-18 61118 Bad Vilbel Germany	PROCTOSAN FORTE, suppository	250 mg	suppository	Rectal use
Romania	STADA ARZNEIMITTEL AG Stadastrasse 2-18 61118 Bad Vilbel Germany	PROCTOSAN, rectal cream	50 mg	rectal cream	Rectal use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Slovakia	STADA Arzneimittel AG Stadastrasse 2 - 18 61118 Bad Vilbel Germany	MASTU S	50 mg / 1 g	Rectal ointment	Rectal use
Slovakia	STADA Arzneimittel AG Stadastrasse 2 - 18 61118 Bad Vilbel Germany	MASTU S forte	250 mg	Suppository	Rectal use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE REVOCATION OF THE MARKETING AUTHORISATIONS PRESENTED BY THE EUROPEAN MEDICINES AGENCY

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING BUFEXAMAC (see Annex I)

Bufexamac is a non-steroidal anti-inflammatory drug (NSAID) authorised for topical treatment of dermatological and proctological diseases, as follows:

- Dermatological
  - to reduce inflammatory symptoms of skin in neurodermatitis and chronic eczema,
  - eczema,
  - pruritus,
  - chronic dermatoses,
  - dermatitis, chronic and subacute,
  - hyperkeratotic conditions, chronic und subacute,
- Proctological
  - acute und chronic anal inflammatory symptoms of skin,
  - anal fissure,
  - acute and chronic anal eczema,
  - inflammatory conditions of anus and rectum,
  - to reduce symptoms of 1st and 2nd grade haemorrhoids.

Medicinal products containing bufexamac are authorised in twelve EU Member States presented as ointment, cream, and/or suppository formulations (see Annex I for the list of bufexamac containing medicinal products authorised in the EU).

On 12 January 2010, the Federal Institute for Drugs and Medical Devices (BfArM) issued a Rapid Alert informing the Members States, the European Medicines Agency and the European Commission in accordance with Article 107 of Directive 2001/83/EC, as amended, of its intention to revoke the marketing authorisations of all bufexamac containing medicinal products for topical use in Germany due to an increased risk of serious allergic contact dermatitis and risk factors for contact sensitisation to bufexamac.

The decision of the German Competent Authority was based on numerous publications and spontaneous reports on contact-allergic reactions following the administration of medicinal products containing bufexamac and recent publications of data on the incidence of and the risk factors for contact sensitisation to bufexamac.

The CHMP considered the matter in accordance with Article 107(2) of Directive 2001/83/EC, as amended during the April 2010 CHMP plenary meeting.

Risk

Bufexamac is used as a non-steroidal antiphlogistic substance for topical treatment of several dermatological and proctological diseases. Numerous case reports of allergic contact-dermatitis after application of bufexamac, partly serious and generalised or requiring hospitalisation, have been collected in ADR databases. The risk of sensitisation has been investigated in various studies published in recent years.

Since the granting of the marketing authorisations, several reviews on these medicinal products have been performed at national levels leading to changes of the Summary of product characteristics (SPC), labelling, package leaflet, or change to the legal status from non-prescription to prescription only medicine. Despite measures being taken at national level in various Member States, the cutaneous effects and particularly the contact allergic reactions, some of which serious, generalised or requiring hospitalisation caused by bufexamac containing medicinal products for topical use have continued to occur.

Updated results of the postmarketing experience regarding the serious allergic contact dermatitis with bufexamac and data from a recent publication on this subject (e.g. *Schnuch A et al.: A common and insidious side-effect: Allergic contact dermatitis caused by bufexamac used in the treatment of dermatitis. Results from the Information Network of Departments of Dermatology (IVDK). Deutsche Medizinische Wochenschrift 2005; Vol 130; 50: 2881-2886*) provide evidence for an increased risk of allergic contact dermatitis in the general population of patients using bufexamac. Additional data on the incidence of contact allergies to bufexamac showed that in a sample of ca. 40.000 patch-tested patients, 1.4% exhibited sensitisation to bufexamac. The following factors were associated with a significantly increased risk for bufexamac sensitisation: anogenital localisation of eczema, other sensitisations, atopic dermatitis, eczema of the legs, female gender, and geographic factors.

In addition, most of the about 450 case reports on bufexamac in National Competent Authority's (BfArM, DE) Adverse Drug Reactions (ADR) database relate to ADRs of the skin or of the immune system, including 189 cases of contact dermatitis. Cases have also been reported in other Member States leading to regulatory actions. Many reports described massive, generalised reactions, some of them requiring systemic treatment with corticosteroids or hospitalisation.

It should also be noted that significant differences between epidemiological data and the number of spontaneous reports on contact dermatitis in the various pharmacovigilance databases clearly suggest significant underreporting and probably underestimation of the frequency of contact-allergic reactions.

Based on the aforementioned data, especially with regard to the clinical manifestation of these ADRs compared with the symptoms to be treated, the CHMP concludes that the clinical picture of the undesirable effects (contact allergic eczema) is identical or very similar to the symptomatology of the disease to be treated (contributing to misdiagnosis, a delay in correct diagnosis and prolongation of the disease). Moreover, the pre-existence of some of the indicated diseases to be treated may constitute risk factors for bufexamac sensitisation. Therefore, the CHMP considers that the exposure to bufexamac increases the risk for the occurrence of contact allergic reactions and even prolong in some cases the duration of the disease.

Risk minimisation measures such as changes to the Product Information (contraindications and strengthened warnings) and/or restriction of availability were proposed by the MAHs in their response document to the List of Questions adopted by the Committee. However, the CHMP maintains the opinion that the proposed risk minimisation measures are not sufficient to substantially reduce or avoid the risk of contact allergy in patient populations treated with bufexamac containing medicinal products.

Therefore, the CHMP is of the opinion that Bufexamac is a potent sensitizer in a high proportion of patients exposed even after short-term use leading to adverse reactions (contact allergies, severe or generalised in some cases) that can not be distinguished clinically from the diseases to be treated leading to misdiagnosis or late correct diagnostic of the allergy and consequently worsening the disease to be treated. In addition the CHMP notes that the pre-existence of some of the indicated diseases to be treated with bufexamac constitute risk factors for bufexamac sensitisation.

Benefit/risk

Bufexamac is used as a non-steroidal antiphlogistic substance for topical treatment of dermatological and proctological diseases. Controlled studies demonstrated lower efficacy of bufexamac than active comparators or no difference to placebo. The CHMP, reviewing evidence from these controlled studies, is of the opinion that, there is only very limited evidence of efficacy for bufexamac in the above mentioned indications. In addition, recent publications on contact allergy *(e.g. Gniazdowska 1999, Waltermamm 2009)*, confirmed that the efficacy of bufexamac in skin diseases is questionable.

The updated results of the postmarketing experience regarding the serious allergic contact dermatitis with bufexamac and data from recent publications on this subject show that bufexamac exhibits questionable efficacy in association with high allergenic potential.

Furthermore, significant differences between epidemiological data and the number of spontaneous reports on contact dermatitis in the various pharmacovigilance databases clearly suggest significant underreporting and probably underestimation of the frequency of contact-allergic reactions.

Taking all these elements into account, the CHMP concluded that the medicinal products containing bufexamac for topical use are harmful under the normal conditions of use, and that the benefit/risk balance for bufexamac is not considered favourable. Therefore the Committee recommended the revocation of the Marketing Authorisations for the medicinal products referred to in Annex I.

GROUNDS FOR THE REVOCATION OF THE MARKETING AUTHORISATIONS

Whereas,

- The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for medicinal products containing bufexamac.

- The Committee concluded, after having reviewed the available data, that bufexamac for topical use is harmful under normal conditions of use due to cutaneous effects and particularly to contact allergic reactions, some of which are serious, generalised or requiring hospitalisation. It is especially of concern that the clinical picture of the undesirable effect (contact allergic eczema) is identical or very similar to the disease to be treated, leading to misdiagnosis, a delay in diagnosis and prolongation of the disease.

- The Committee noted that the pre-existence of some of the indicated diseases to be treated with bufexamac may constitute risk factors for bufexamac sensitisation and serious hypersensitivity reactions.

- The Committee considered the benefit-risk ratio of bufexamac under the normal conditions of use and considered that the aforementioned evidenced risk of contact allergic reactions is not acceptable, taking into account that the efficacy of bufexamac is limited in the treatment of dermatological and proctological diseases. In addition, the Committee considered that the proposed risk minimisation measures are not appropriate to reduce the risks to an acceptable level.

- The Committee, in light of the above findings, concluded that the benefit/risk balance of bufexamac containing medicinal products for topical use is not favourable under the normal conditions of use.

Following the provisions under Article 107(2) of Directive 2001/83/EC, as amended, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommends the revocation of the Marketing Authorisations for all bufexamac containing medicinal products listed in Annex I.