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Assessment report for buflomedil-containing medicinal products

Procedure number: EMEA/H/A-107/1293

Procedure under Article 107 of Directive 2001/83/EC, as amended

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 11 February 2011, France informed the EMA of the suspension of the Marketing Authorisations of buflomedil-containing products in its Member State. A procedure under Article 107 of Directive 2001/83/EC, as amended was automatically initiated for buflomedil-containing medicinal products.

2. Scientific discussion

2.1. Introduction

2.1.1. Background

Buflomedil is an α1-, α2-adrenolytic agent with vasoactive and haemorheologic properties, increasing the peripheral and cerebral blood flow in impaired vascular beds, particularly at the microcirculatory level (pre-arterioles) by inducing vasodilatation without affecting the systemic blood pressure. Buflomedil is known to inhibit platelet activation and aggregation by reducing adenosine diphosphate (ADP) and collagen-induced platelet aggregation. Buflomedil is also known to act on the red cell membrane, improving its elasticity. As a result, buflomedil improves the blood flow in the microcirculation as well as tissue oxygenation. Buflomedil-containing medicines are authorised and marketed in 12 EU countries by national procedures and were first authorised in France in 1974. Buflomedil containing medicines are available as 150 and 300 mg immediate release (IR) tablets or as a 600 mg sustained release tablet (SR), as solution for injection 10mg/5ml and as an oral solution.

The currently approved indication in France is the treatment of ”symptomatic peripheral arterial occlusive disease (PAOD Stage II) symptoms”. In other member states, variations have been submitted to restrict the indication, in line with the one approved in France. The approved posology in patients with normal renal function is 150 or 300 mg every 12 hours, with a maximum daily dose of 600 mg. In some member states, the dosage is achieved through administration of a single 600 mg SR tablet. In patients with renal impairment, the maximum daily dose is 300 mg. For i.v. administration, the recommended posology is 50 mg to 200 mg per day in divided doses. Usage of buflomedil according to these conditions is considered to be under normal conditions of use.

France previously conducted three pharmacovigilance and toxicovigilance investigations, in 1997 (covering the period since first authorisation), 2005 (covering the period 1998-2004) and 2010 (covering the period 2007-2009) respectively, following notification of nervous system and cardiac serious adverse events (SAEs) associated with the use of buflomedil. In these enquires, the reported nervous system SAEs consisted mainly of convulsions, myoclonia and status epilepticus while the cardiac SAEs consisted mainly of tachycardia, hypotension, ventricular rhythm disorders and cardiac arrest. The results of these investigations have shown that nervous system and cardiac SAEs occurred in intentional overdose as well as under normal conditions of use, including in accidental overdose (mainly in patients with impaired renal function and in elderly patients).

Following the two first enquiries, France took a number of national regulatory actions to minimise the risk of adverse events associated with buflomedil. The risk minimisation measures taken as a result of the 1997 enquiry included:

- a reduction of the number of tablets per pack;
- a recommendation of lowered posology in patients with hepatic and renal insufficiency and;
- information to emergency physicians describing acute symptoms in case of buflomedil overdose.

The risk minimisation measures taken as a result of the 2005 enquiry included:

- the withdrawal of the 300 mg strength;
- a restriction of the indication of buflomedil to the” improvement of peripheral artery occlusive disease (PAOD) symptoms”, with the deletion of the indication for “improvement of Raynaud’s phenomenon”;

- the addition of a contraindication in severe renal impairment, together with dose adaptation in mild to moderate renal impairment and regular control of renal function and the addition of “narrow therapeutic margin” to the Summary of Product Characteristics (SmPC).

A drug utilisation study to assess the impact of these risk minimisation measure (Thalès study) was also conducted, as discussed in the risk minimisation measures section of this assessment report. Both enquiries were followed by communications to healthcare professionals. However, subsequent investigations suggested that the risk profile of buflomedil remained unchanged.

In May 2010, in the context of the assessment of the Periodic Safety Update Report (PSUR), Portugal circulated a Preliminary Assessment Report (PAR) based on a full analysis of the benefit-risk of buflomedil in the approved indications carried out by Amdipharm, the Marketing Authorisation Holder (MAH) of the originator product, who acquired the licences in a number of countries from Abbott Laboratories in May 2008.. The MAH report reviewed all available individual case safety data relating to buflomedil. The PAR assessed the specific safety concerns raised by the PSUR report of 22 June 2009 and the primary aim of the report was therefore to review and present all the individualised cases of injury, poisoning and procedural complications, cardiac, nervous system and psychiatric manifestations reported that resulted from overdose (accidental or intentional), suspected poisoning and intoxication potentially associated with buflomedil drug toxicity, leading to an overall assessment of the benefit-risk balance of buflomedil. As a result of this PAR, variations were requested and submitted in most concerned member states, together with Dear Healthcare Professional Communications (DHPCs) in some member states. The variations introduced the restriction of the therapeutic indications to the symptomatic treatment of intermittent claudication, warnings reinforcing its narrow therapeutic margin and the adjustment of the dosage in patients with renal insufficiency and the need to determine renal function before and regularly during treatment. In addition, the wording “Patients with a history of depression and/or a history of drug overdose should be monitored closely when prescribed buflomedil” was added to section 4.4 of the SmPC. These changes were largely similar to the changes already introduced in the SmPC of products marketed in France and at the time of the finalisation of the benefit-risk assessment, France commented that no improvement of the safety profile had been observed in France after the implementation of the 2006 Risk Management Plan (RMP).

In December 2010, a further French benefit-risk evaluation of buflomedil was carried out, covering the 2007-2009 period, following which the French national advisory board issued a negative opinion on the benefit-risk balance of buflomedil-containing products on 27 January 2011. As a result, the French National Competent Authority (AFSSAPS) suspended all French Marketing Authorisations (MAs) for buflomedil-containing products on 11 February 2011, due to safety concerns, based on the observed neurological (convulsions, myoclonia and status epilepticus) and cardiac (tachycardia, hypotension, ventricular rhythm disorders and cardiac arrest) SAEs. All batches were recalled on 17 February 2011. As a result, a procedure under Article 107 of Directive 2001/83/EC, as amended was automatically initiated for buflomedil-containing medicinal products. The procedure started during the February 2011 CHMP meeting and a list of questions was adopted and sent to all Marketing Authorisation Holders (MAHs).

Although there are more than 30 MAHs for buflomedil-containing products in the EU, only 9 were actively involved in the procedure, and only Amdipharm (referred to as the MAH) provided extensive answers to the questions raised. The CHMP assessment takes into consideration responses provided by the MAHs, all French national enquiries, including the benefit-risk assessment performed at the French national level in 2010-2011, as well as an analysis of cases from EudraVigilance database.

2.1.2. Peripheral Arterial Disease

Peripheral vascular disease (PVD), commonly referred to as peripheral arterial disease (PAD) or peripheral artery occlusive disease (PAOD), refers to the obstruction of large arteries which are not within the coronary/aortic arch vasculature or brain. PVD can result from atherosclerosis, inflammatory processes leading to stenosis, an embolism, or thrombus formation. It causes either acute or chronic ischaemia (lack of blood supply). The term PAOD is often used to refer to atherosclerotic blockages found in the lower extremities of the body. PVD also includes a subset of diseases classified as microvascular diseases resulting from episodic narrowing and widening of the arteries leading to Raynaud’s phenomenon and vascular spasms. Epidemiologically, the prevalence of PVD in the general population is 12–14%, affecting up to 20% of those aged over 70. The incidence of symptomatic PVD increases with age, from about 0.3% per year for men aged 40–55 years to about 1% per year for men aged over 75 years. PVD affects 1 in 3 diabetics over the age of 50. 70-80% of individuals with

PVD are asymptomatic, with only a minority requiring revascularisation or amputation. A likely association between renal insufficiency and PAOD has been identified, which some recent evidence suggest may be causal. In the HERS study (Heart and Estrogen/Progestin Replacement Study), renal insufficiency was independently associated with future PAOD events in postmenopausal women.

Risk factors for peripheral arterial disease are the same as those for atherosclerosis: hypertension, diabetes, dyslipidemia, tobacco use, diabetes, and a family history of atherosclerosis. Obesity, male sex, and a high homocysteine level are also risk factors. Typically, PAOD causes intermittent claudication (IC), which is a painful, aching, cramping, uncomfortable, or tired feeling in the legs that occurs during walking and is relieved by rest. Claudication is a manifestation of exercise-induced reversible ischemia, similar to angina pectoris. As PAOD progresses, the distance that can be walked without symptoms may decrease, and patients with severe PAOD may experience pain during rest, reflecting irreversible ischemia. Patients with PAOD therefore typically have multiple cardiovascular risk factors, putting them at a markedly elevated risk of cardiovascular events. The majority will eventually die of a cardiac or cerebrovascular cause; prognosis is correlated with the severity of the PAOD.

The management of PVD is dependent on the severity of the disease and the following steps can be taken: Smoking cessation; weight reduction; management of diabetes; management of hypertension; management of cholesterol and medication with anti-platelet drugs. As part of the initial treatment strategy for patients with IC, regular exercise to help open up alternative small vessels (collateral flow) should be included. Treadmill exercise or track walking of sufficient intensity to bring on claudication, followed by rest, has been reviewed as another treatment with a number of positive outcomes including reduction in cardiovascular events and improved quality of life. However, some patients may have contraindication for exercise (e.g. severe CAD, musculoskeletal limitations or neurological impairments). Medications which reduce clot formation and cholesterol levels can therefore help with disease progression and address the other cardiovascular risks that the patient is likely to have. Drug therapy for relief of symptoms typically involves different drugs than those that would be used for risk reduction. Vasoactive drugs, such as buflomedil, are used as symptomatic treatment and adjunctive therapies, or as second-line therapy when other treatments (anti-hypertensive, anti-diabetic) have failed to produce an adequate response.

In summary, the treatment of PVD must take into consideration the management of associated cardiovascular risk factors and their complication through well-recognised and essential therapies such as treatment of diabetes, hypertension, cholesterol, anti-platelet medication. Smoking cessation is also an important measure to reduce the CV risk while regular exercise, notably with treadmill programme, could also be useful in reducing symptoms of intermittent claudication.

2.2. Discussion on safety

In order to assess the main risks associated with buflomedil i.e. serious cardiac (mainly tachycardia, hypotension, ventricular rhythm disorders and cardiac arrest) and neurological (mainly convulsions, myoclonia and status epilepticus) adverse events, the MAH provided a detailed analysis and discussion of the available data, including pre-clinical studies, clinical trials, post-marketing spontaneous reports, and published literature. Information on the seriousness, the frequency and the outcome of the observed reactions was also provided.

2.2.1. Non-clinical data

2.2.1.1. Preclinical studies

The original animal preclinical studies supporting the Marketing Authorisation approvals were completed by 1988; an overview of both the preclinical original studies and more recent literature reports with particular reference to neurological and cardiac toxic effects were provided by the MAH. Acute, subacute and chronic toxicity investigations were conducted using a number of animal species including mice, rats, rabbits and dogs, studying oral and parenteral administration, at various dosage levels. Buflomedil was found to be well tolerated in mice (the lethal minimum dose (LMD) was 168 mg/kg) and rats (LMD = 300 mg/kg) but less tolerated in dogs and rabbits, in which convulsions and immediate death were found at doses > 20 mg/kg in rabbit. Convulsions, vomiting and apnoea were found in dogs at 66 mg/kg. Epileptiform seizures were reported in all of the 4 species, with fatal outcomes in a number of the studied animals. In general, fatal epileptiform seizures were almost simultaneously accompanied or immediately preceded by respiratory and cardiac arrest. In surviving

animals, withholding the drug resulted in complete resolution of the toxic effects, confirming that the use of buflomedil resulted in no lasting effects. The mechanism of the development of the described events is unclear and its relationship to the physiochemical characteristics of the drug is unknown. Overall, the major signs of overt toxicity induced by buflomedil following subacute and chronic IV and oral administration in rats and dogs were convulsions and death, which were usually observed within minutes following drug administration in the affected animals. Where it was measured, death was also preceded by a fall in blood pressure. While buflomedil passes the blood brain barrier, the mechanism of action on the central nervous system is unknown. The kidney seems to be a target organ for concentration of buflomedil: indeed, an increase in kidney weight was seen in male rats in the 3 months study and in the 12 months study at 400 mg/kg/day. In a few dogs, chronic tubular nephritis was seen in the 6 months study at high doses (60 mg/kg/day).

The MAH concluded that the toxic effects and in particular those affecting the central nervous system (ataxia, apathy, clonic movement, epileptiform seizures) related to the use of buflomedil in the tested animals are species specific (affecting dogs and rabbits only and at 6 times the maximum dose in clinical use). However, there were inter-individual variations of susceptibility within the two susceptible species. The preclinical studies provide no evidence of a primary cardiac effect, with death in all species being related to neurotoxicity. Histological observations suggest that such serious effects could be triggered acutely by a high dose of the compound that could mediate yet unknown mechanisms that cause the observed serious events. The toxicokinetics of buflomedil in the dog have been explored very recently in a study commissioned by Amdipharm, although the final report is not yet available.

2.2.1.2. Published literature

The MAH conducted a PubMed search in March 2011, obtaining 56 hits, 42 of these from 1988 or later. All were reviewed for relevance to the safety of buflomedil and for any neurological or cardiac effects in particular. The MAH concluded that the studies published in the literature do not provide any mechanistic explanation for the observed neurotoxic effects. Doses of 10-30 mg/kg were found to have an emetic activity in the dog which was inhibited by domperidone. Catalepsy was induced in mice at doses over 120 mg/kg and was blocked by l-dopa suggesting that buflomedil may induce emetic action as a dopamine agonist at a low dose, whereas it acts as a dopamine antagonist and a catalepsy inducer at high concentrations.

2.2.1.3. Overall summary of non-clinical data

The CHMP noted the MAH review of all available preclinical data, including data submitted in the original MAA dossier and data from literature retrieved via Pubmed. The original preclinical studies showed no significant histological changes in tested animals (acute or chronic exposure) and no evidence of a primary cardiac effect was identified. The kidney appeared to be a target organ of concentration for buflomedil.

The CHMP noted that toxic effects, in particular those affecting the central nervous system were observed in dogs and rabbits (at 6 times the maximum dose recommended in clinical use) while buflomedil was well tolerated in mice and rats (with 40 times of the maximum dose recommended in clinical use). The effects were therefore considered to be species specific. The major signs of toxicity induced by buflomedil in rats and dogs were convulsions and death. Death in all species is related to evidence of neurotoxicity.

In conclusion, from preclinical studies and from published literature, only the neurological toxicity observed at high doses in mice and rats and at lower doses in dogs was considered to be relevant to human use.

2.2.2. Pharmacokinetic data

The MAH submitted a summary of a study on the effect of age on pharmacokinetics. The study compared the plasma concentration-time curves of 12 young (18 to 36 years) and 16 elderly (65 to 72 years; mean: 68 years) subjects following oral administration of buflomedil (two 300 mg doses, 12 hours apart). The results suggested that plasma clearance decreases with age. Mean Cmax (2.32 vs. 1.73 mg/L*)* and AUC 0-24 (27.3 vs. 18.3) were significantly increased ($p=0.01$ and $p=0.002$, respectively) in the elderly subjects and were significantly correlated with age ($p=0.02$ and $p=0.003$, respectively). The CHMP noted that no dose ranging study was performed in the context of the MA

application, and that buflomedil has been used at daily dosages of 50 mg to 400 mg for the IV route and from 300 mg to 600 mg for the oral route.

The CHMP also noted data suggesting that the elimination of buflomedil is impaired in patients with renal failure. A comparison between intravenous administration of 100mg of buflomedil hydrochloride salt to patients with renal insufficiency with published data on healthy subjects using the same dose showed a significant decrease in renal clearance, renal elimination percentage (6.6 vs. 21.4%) and a significant increase in the elimination half-life from the central compartment (3.9 vs. 0.7 h). In patients with liver disease, the elimination of buflomedil was impaired in patients when administered orally, but no significant differences in pharmacokinetic parameters were detected in patients who received the drug intravenously, compared with values in healthy subjects. With regards to diabetes, the pharmacokinetic profile of buflomedil following oral (300 mg) and intravenous (100 mg) administration seem to indicate that the metabolism of buflomedil is inhibited in diabetic patients. The CHMP noted that the French SmPC was amended in 1998 in order to recommend a lower posology in patients with hepatic and renal impairment and that in 2006, an additional contraindication in severe renal impairment, dose adaptation in mild to moderate renal impairment and regular renal function monitoring were added.

At the request of the Italian Regulatory Authority, two new studies were conducted to address concerns regarding the relative toxicity of the 600 mg dosing form, a sustained release formulation to be taken once daily. The first was a pharmacokinetic study in volunteers to compare the 600 mg SR tablet and the 300 mg IR tablet and the second a toxicokinetic study conducted in dogs to examine the effects of dosing at around ten times the effective human dose. The conclusions from the pharmacokinetic study were that the test and the reference formulations were safe and well-tolerated and that exposure (AUC and Cmax) to buflomedil was equivalent between the two formulations. The rate of absorption of the SR formulation was also shown to be lower compared to that of the immediate IR formulation as evidenced by a 2.6 hours delay in tmax. A simulation of buflomedil plasma levels after repeated administration of 600 mg buflomedil SR once a day or 300 mg of buflomedil IR twice a day (12 hours apart) suggested that in steady state conditions, the exposure is similar for the two formulations. The dosing in this study has been concluded, however a few assay results are awaited before the study report and conclusions can be prepared. The final results are therefore not yet available.

2.2.3. Discussion on clinical safety

2.2.3.1. Clinical studies

The historical data available for review by Amdipharm were either transferred to Amdipharm from Abbott's archives accumulated over the years or obtained from available published literature. The MAH submitted the clinical expert report written in 1988 as part of a MA application in an EU MS, which summarises all available clinical trials sponsored by Abbott or available from literature. The MAH compiled data from 17 buflomedil studies, 13 double-blind and 4 open, including a total of 791 patients. Of these patients, 442 patients received buflomedil (450 or 600 mg/day), 266 patients were treated with placebo and 83 with an alternative compound (active control). Overall, 114/442 (26%) of buflomedil treated patients reported one or more adverse events. In double-blind placebo controlled studies (11 out of 17), the incidence rates were 30% and 32% for buflomedil and placebo patients, respectively. In active-controlled studies, the incidence rates were 14% for buflomedil and 23% for active control patients. The signs and symptoms reported most frequently by buflomedil patients were vertigo (5%), headache (4%), vasodilation (3%), GI discomfort (3%), dizziness (3%) and nausea (2%). All of these, except for vasodilatation and vertigo, were reported in similar proportions by the placebo patients.

2.2.3.2. Post-marketing data

Overview of the data

A number of analyses of post-marketing data were considered by the CHMP, including a review of Eudravigilance data, two reviews carried out by the MAH, focusing on serious adverse events under normal conditions of use and in overdose, respectively, as well as French Pharmacovigilance enquiries. When assessing the data, the CHMP also noted data from cases of intentional overdose and off-label use, which cannot be considered as normal conditions of use. These cases were therefore not taken

into account in the conclusions on the benefit-risk assessment of buflomedil. As data from a number of sources was assessed, duplication of cases is expected and acknowledged.

The CHMP noted a review of French Eudravigilance data, in which spontaneous reports associated with treatment with buflomedil were analysed. In particular, cases where cardiac and neurological reactions occurred under normal therapeutic doses (i.e. maximum of 600 mg daily for the oral tablet formulation) were reviewed. Using a cut-off date of 28 March 2011 and restricting the dataset to French cases and after removing duplicates and reports related to other ADRs than the ones constituting the main focus of the analysis, 74 cases were retained.

The MAH conducted a review of the ICSR database (Abbott and Amdipharm), identifying 462 reported cases since the initial marketing authorisation. Cases reporting cardiological or neurological adverse events under normal conditions of use were selected, i.e. cases where the dose did not exceed the maximum daily dose of 600mg, cases with accidental overdoses or cases including patients with known renal impairment requiring dose adjustment. A total of 54 cases matched these criteria.

The MAH also conducted a review of all available individual case safety data relating to buflomedil. Post-marketing safety data related to buflomedil intoxication was collected from Abbott Laboratories' global safety database and Amdipharm's safety database, published medical literature (worldwide) and from a number of other sources, including Toxicology/Poison Control Centres and Regulatory Authorities. A total of 728 cases of SAEs with buflomedil were retrieved, of which 223 met the selection criteria (causality, sufficient information, clinically significant adverse events). Each case represents a single patient. 45 of these cases were non-overdoses, leaving 178 cases with an increased exposure to buflomedil, from 11 countries. The patients were mainly from France (52.8%) and from Germany (32.5%). The MAH presented the clinical adverse events (using MedDRA Preferred Terms - PTs) resulting from overdose (accidental or intentional), suspected poisoning and intoxication potentially associated with buflomedil, classified under four System Organ Class of Interest (SOCIs): i) Injury, poisoning and procedural complications, ii) Cardiac disorders, iii) Nervous system disorders and iv) Psychiatric disorders.

Serious cardiovascular and neurological adverse events under normal conditions of use

From the 74 selected French EudraVigilance cases associated with treatment with buflomedil, a total of 35 cases recorded cardiac adverse events (mainly atrial fibrillation, hypotension, bradycardia, malaise and cardiac arrest). After excluding cases that were too poorly documented to assess, duplicates and cases considered to be unlikely to be associated with buflomedil, 6 cases were identified, involving renal failure and/or increased plasma levels of buflomedil that may be associated with adverse events. Although the cases were confounded by clinical history and/or concurrent medications, harm under normal conditions of use cannot be excluded and therefore constitute a signal.

The other 39 cases recorded neurological adverse events (mainly epilepsy, myoclonus, seizures and convulsions). After removing duplicates and cases that were too poorly documented to assess 6 cases remained, involving renal failure and/or increased plasma levels of buflomedil that may be associated with adverse events. Although the cases are confounded by clinical history and/or concurrent medications, harm under normal conditions of use cannot be excluded and therefore constitute a signal.

A sub-analysis of the 77 non-French EU cases focused on 39 cases that involved fatal or adverse cardiovascular and neurological outcomes. The majority of the cases were from Germany (12) and Italy (16) and were too poorly documented, particularly in terms of the therapeutic indication or dose, to inform on causality.

In conclusion, a total of 12 cases were identified in Eudravigilance in which patients were treated within the maximum therapeutic range (i.e. up to 600 mg daily) of buflomedil and experienced serious cardiovascular or neurological adverse events. There were 6 cases of cardiovascular (mainly atrial fibrillation, hypotension and malaise) and 6 cases of neurological (mainly myoclonus, epilepsy and convulsions) serious adverse events. Although the 12 cases were complicated by underlying clinical conditions and other concomitant medications, the CHMP considered them to confirm the risk of serious adverse events associated with the use of buflomedil under normal conditions of use.

Among the 54 cases identified in the MAH review of the ICSR database, 33 cases (retrieved from a total of 219 cases of non-overdose) involved the use of a maximum daily dose of 600 mg. From these, a total of 21 neurological adverse events were retrieved. One case of convulsion and 2 cases of

myoclonus were reported, together as well as dizziness, tremor, and balance disorders. The case of convulsion occurred in a patient who took two 300 mg tablets at the same time instead of two tablets BID. The CHMP was of the opinion that this data showed the risks associated with buflomedil in view of its narrow therapeutic margin.

In addition, a total of 32 cardiological adverse events under normal conditions of use were retrieved by the MAH. The most frequent reactions were tachycardia, hypertension, flushing and hypotension. Cases of torsade de pointes, cardiac arrest and cardiac failure were also reported. Tachycardia, hypotension and rhythm disorders are already listed in the SmPC but mainly in relation to overdose situations.

The 33 cases (out of 219) represent 15% of all adverse reactions occurring at therapeutic doses up to 600 mg and associated with cardiac or neurological events. This percentage is identical to the one observed in cases of accidental overdose (15 out of 94, i.e. 16%), indicating that the profile of adverse reactions is similar irrespective of the circumstances, at therapeutic doses or in patients accidentally overdosed.

Serious cardiovascular and neurological adverse events in elderly patients and patients with renal impairment

Among the 54 cases identified in the MAH review of the ICSR database, 5 cases with known dosage occurred in elderly patients for whom dosage adjustment was required. All patients were aged between 83 and 89 years, and in four cases, renal impairment was reported. The reported ADRs were mainly related to serious neurological and cardiovascular ADRs including cardiogenic shock, grand mal convulsion, angina pectoris, myoclonia and coma. In addition to these 5 cases, a further two cases related to renal impairment were identified, where the dose was unknown, bringing the total number of cases of renal impairment to 7 cases.

Based on the MAH review of all available individual case safety data (MAHs databases, published literature, others) 14 out of the 178 (8%) selected cases reported increased exposure in elderly patients receiving chronic prescribed doses of buflomedil that were not adjusted for age and renal status. This included 12 cases from a single publication (*Bruhat et al., 2004 - Buflomedil overdosage with quantitative analysis in the elderly. Fund & Clin Pharm.18:215-268*). The patients subsequently demonstrated elevated plasma levels of buflomedil corresponding to overdose and subsequent cardiovascular and neurological toxicity. The outcome was recorded as recovered in all cases.

In addition, 28 of the 178 selected cases reported overdoses in elderly patients (over 65 years of age). Within these reports, 3 patients died, 22 patients recovered and the outcome was unknown in 3 patients. Among the cases recording recovery or unknown outcome, 6 cases were recorded as accidental overdose and 3 cases as intentional overdose (respectively 3-6 g, 6 tablets of 150 mg, 3g). 12 of the cases were the ones described in the above-mentioned publication by Bruhat et al.. Buflomedil plasma levels were reported in the range of 2.6 - 10 mg/L (upper therapeutic level: 3 mg/L) and it was noted that in 70% of the cases, the dose of buflomedil received by the patients was inappropriate because of the underlying renal failure and in one case due to the concomitant use of cytochrome 2D6 inhibitors.

The CHMP noted that in case of renal impairment or in elderly patients, CYP2D6 inhibition could cause an increase in plasma concentration of buflomedil leading to an increase of ADRs (mainly neurological).

The outcome of two French pharmacovigilance enquiries covering the period 1998 to 2004 and 2006 to 2009 were also noted. These reported 188 (99 males and 89 females) and 26 (15 males and 11 females) patients respectively who experienced AEs with or without misuse, accidental or intentional overdose. The mean age was 70.2 and 71.6 years, respectively. Around 50% of the patients in both French enquiries were over 80 years. Despite the minimisation measures taken to reduce the risk of accidental overdose in elderly patients, including dose adjustment and regular control of renal function, the risks remain unacceptable.

Serious cardiovascular and neurological adverse events with overdose

The MAH review of the ICSR database identified 16 cases (from a total of 94 cases of accidental overdoses) associated with cardiovascular or neurological ADRs, although only 13 cases (81%) were specifically mentioned reported as accidental. In two cases, it was only reported as overdose, and in

one case no information was reported. The ingested dose varied between 150mg and 2325 mg. For the 13 confirmed accidental overdose cases, the age of the patient was known in 12 cases and unknown in one case. In six cases, patients were aged between 75 and 84 years, in four cases patients were aged between 2 and 4 years. In the remaining two cases, patients were aged 15 and 23 years old. The ADRs reported for the 12 cases were neurological in 7 cases (mainly represented by convulsion) and cardiovascular in 3 cases (rhythm disorders and hypertension), with two cases reporting both neurological and cardiological ADRs. One case of accidental overdose reported vomiting and abdominal pain, where the cardiac and neurological ADRs were missing. For the purpose of its review the CHMP did not consider the overdose cases in children and young adults. However, the CHMP considered that these data are of significant concern as they show that accidental overdoses occur mainly in the elderly population in which buflomedil is recommended.

Based on the MAH review of all available individual case safety data (MAHs databases, published literature, others), 178 cases of overdoses were also identified. 54 cases of nervous system disorders were reported, with 8 patients experiencing coma and 36 experiencing seizures. No explanation was provided for the ten remaining patients. For the 44 described patients, 4 indications were known: vasculopathy, post-embolectomy, arteritis, lower limb arteriopathy. The amount of buflomedil was between 600 mg and 3g. The medical history was reported in only 6 of the 36 patients who experienced seizures, including one case of renal insufficiency). There were two reported cases of concomitant consumption of alcohol resulting in a coma.

In addition, 27 patients experienced both serious adverse neurological and cardiac disorders. 7 patients experienced cardiac arrest and 20 patients experienced various forms of arrythmias. 19 of these patients also experienced seizures and 10 patients also suffered comas. There was a lower number of cases presenting cardiotoxicity as compared to neurotoxicity and generally, the occurrence of the neurological adverse events preceded the emergence of the cardiologic adverse reactions. In all of these cases, the indication was unknown or off label use. The majority of patients should have been monitored.

32 of the 178 cases of overdose (18%) were recorded as having a fatal outcome. In these cases, the minimum quantity of buflomedil ingested was reported to be 3 g (of oral drops) in one case and 3.9 g (of 150 mg tablets) in another. The maximum was 24 g in two cases. Most fatal cases were reported in patients ≤40 years of age who were receiving buflomedil for unknown indications, likely to be off-label. The signs of nervous system toxicity in the majority of cases were seizures and coma and the signs of cardiac toxicity were cardiac arrest and various forms of arrhythmias. No particular correlation was noted between the occurrence of these events and the ingested amount of buflomedil.

Paris Poison Control Centre

The CHMP noted the data from the Paris Poison Control Centre (CAPP) for the period November 1976 to June 1981, consisting of 26 cases of acute toxic reactions to buflomedil. The 26 subjects involved ranged from 14 months to 58 years of age. Doses of the drug ranged from 150 to 9,000 mg (1 to 60 tablets). The symptoms were peripheral vasodilation, sinus tachycardia, vomiting, somnolence, coma (Stage I-II), agitation and convulsions.

Lyon Anti-poison and Toxicovigilance Centre

The CHMP reviewed the MAH responses and the data compiled by the Lyon Anti-poison and Toxicovigilance Centre (CAPTV) on accidental (domestic or therapeutic errors) and intentional (drug addiction or suicide attempt) overdose cases in France, covering the period 1998 to 2004 as well as the period 1 January 2007 to 31 December 2007 as well as a follow-up study for the period 1 January 2008 to 31 December 2008. 341 were reported in the reference study, 55 cases in 2007 and 46 in 2008. The number of overdoses increased during the period 2000 to 2003 and then dropped again in 2007 and 2008, possibly as a result of the increased attention given to the product. In 2007, the year after the French withdrawal of the 300 mg tablet, the number of overdoses decreased, only to increase again in 2008. Regarding the occurrence of therapeutic errors, the CHMP noted that among the 26 cases reported in 2007, 11 were reported with the 300mg dosage despite of the withdrawal of this presentation. In 2008, at least four of the 14 serious cases involved the 300 mg tablet formulation. One of these four cases resulted in a fatal outcome. With regards to distribution of cases by age and sex, 55.1% of cases were reported in patients ≤40 years of age and 44.8% in patients over 40 years of age. 65.3% of cases were reported in female patients and 34.6% in males. The CHMP noted that more than two years after the initiation of the risk minimisation measures, occurrences of severe overdoses persist.

The CHMP also noted the total data from all French PCCs, as compiled by the Lille Poison Control Centre from the date of initial marketing authorisation until the end of 1996. In total 220 cases were observed, 44 cases were classified as serious and among them, 43 were intentional overdoses (suicide attempts). A second enquiry was conducted over the period 1998 to 2005. The Lyon PCC compiled 376 cases of acute toxicity reactions of which 223 cases (60%) were intentional overdoses (222 suicide attempts) leading to a fatal outcome in 24 cases. A third enquiry conducted during the period 2008 to 2009 by the Lyon PCC compiled 101 cases of which 21 cases (20%) were intentional overdoses leading to death in 3 cases. The CHMP noted that although a large number of cases of adverse events were linked to intentional overdoses, a significant number of cases could possibly be attributed to accidental overdose.

German Poison Control Centre

The CHMP noted the data from the German Poison Control Centre (GPCC) in Bonn (which records cases from Germany, Austria, Belgium and Switzerland) on a total of 87 cases. After exclusion of cases reporting adverse events already identified with normal therapeutic doses of buflomedil, cases where an adverse event was considered to be clinically non-significant and cases in which buflomedil was considered to be causally unrelated to the adverse event were excluded, together with any duplicate case reports, a total of 62 cases were shortlisted for further analysis. 46 of these were recorded as intentional overdoses, 10 as accidental overdoses, 5 as overdose and 1 as 'suicide attempt'. The submitted GPCC data covered the period 1986 to 2009, representing 13 years of data and the 62 overdose cases (including the 10 cases of accidental overdose) therefore translate into an average of 2.8 cases of overdoses per year. The number of overdose reports increased from the period from 1986 to 1999 (2.1 cases/year) to the period from 2000 to 2009 (3.7 cases/year). Even though under-reporting is generally expected with old medicines, the observed increase in the rate of overdose reports is unexpected and of concern.

2.2.3.3. Overall conclusions on clinical safety

In summary, the CHMP concluded that the use of buflomedil is associated with a number of serious cardiological (mainly tachycardia, hypotension, ventricular rhythm disorders and cardiac arrest) and neurological (mainly convulsions, myoclonia and status epilepticus) adverse events, which occur under normal conditions of use, particularly in elderly patients, who are predominantly the patient population relevant to the approved indication. These risks are compounded by the fact that buflomedil is a substance with a narrow therapeutic index and that buflomedil treatment requires dose-adaptation to adjust for renal function. If dose-adaptation is not done correctly, this leads to serious and life-threatening toxicity. This is of particular concern as patients with peripheral vascular disease are inherently likely to experience decreased renal function due to the nature of their condition.

2.2.4. Safety of the injectable formulations of buflomedil

The CHMP also carried out a separate assessment of the safety of the injectable formulations of buflomedil. Buflomedil solutions for injection or solutions for infusion are authorised in 8 member states and are used in the hospital setting for the treatment of severe chronic ischaemia of the lower limbs in patients at risk of amputation and in which revascularisation through surgery or angioplasty have failed, could not be performed or were not indicated. The products are used in the most critical PAOD (stage III or IV), in emergency. The expected treatment course would start patients on parenteral formulations of buflomedil and later switch them to the oral formulation and most study designs therefore used an initial injection therapy, IM or IV, for 7-30 days, followed by oral therapy for short, medium-term and long durations. The CHMP therefore considered that a completed course of treatment of severe PAOD could be assumed to include both formulations of buflomedil. In the context of the 2006 French benefit-risk review, it was considered that the available clinical studies with the parenteral formulation were old (1979-1989) and of poor methodological quality. The main MAH in France (Cephalon) was therefore requested to conduct a controlled study assessing the efficacy of buflomedil by IV route in patients with stages III and IV PAOD. However, Cephalon was not able to perform the requested study and decided to withdraw the licences in France on 1st January 2008. In addition, the CHMP was informed during its July 2011 plenary meeting of Amdipharm's intention to withdraw its parenteral formulation products.

Postmarketing spontaneous reports

The MAH identified a total of 24 cases with the buflomedil solution for injection formulations in the global buflomedil ICSR safety database, which contains cases reported by Healthcare Professionals,

Consumers and Regulatory Authorities and includes cases obtained from Poison Control Centres. The MAH presented the cases divided into three main categories.

A) Allergic reactions (including Anaphylaxis/ Anaphylactic reaction)
A total of 6 patients experienced allergic reactions when treated with parenteral (IV and IM) formulations of buflomedil. Allergic reactions are listed with the use of injectable buflomedil. There were no fatalities reported. In 4 cases, the patients developed allergic reactions within a few minutes of receiving buflomedil injection. In the remaining 2 cases the temporal relationship could not be established clearly.

B) Medication error (including accidental overdose)
A total of 13 cases classified as medication errors / therapeutic errors have been reported, in which patients may have received an accidental overdose of buflomedil when the recommended maximum daily dose of buflomedil (IV/IM) of 200 mg daily has been exceeded. In at least three cases, the patients had a known history of renal impairment which implies that buflomedil administration should have been adjusted/contraindicated. There were 2 fatal cases, in which buflomedil was administered at at least twice the daily recommended maximum therapeutic dose. Buflomedil solution for injection was administered at at least twice the daily recommended maximum therapeutic dosage in 12 cases. Five patients experienced cardiological serious adverse events and 4 neurological adverse events. A misuse with indication was identified in two patients.

C) Other - Isolated cases
5 other cases have been reported with the injectable form of buflomedil. One patient reported somnolence, a listed event for buflomedil. Another patient experienced ecchymosis which was assessed as unrelated to buflomedil by the reporter. Similarly, in the remaining three cases, the patients were co-medicated with drugs for which the events observed were listed reactions.

In summary, the CHMP noted the 24 cases, considering the data to be of low quality, mainly because of the inherent limitations of spontaneous reporting. The CHMP considered that the 4 cases of cardiovascular adverse reactions, the 4 cases of neurological adverse reactions and the case reporting both cardiovascular and neurological adverse reactions adds to the evidence of the risks associated with buflomedil. Four cases were noted in particular, involving patients aged between 66 and 74 years who received twice the daily recommended maximum dosage of buflomedil injection (i.e. 400mg/day) and experienced various toxic cardiovascular symptoms. The outcome of one of the cases was fatal. The CHMP agreed in principle that these elderly patients are expected to have significant pre-existing cardiovascular history and receive multiple concomitant medications and that an overdose was administered. Nonetheless, the adverse events were of concern and support the knowledge of the safety profile of buflomedil in case of accidental overdose and overall safety profile as the CHMP also noted that the adverse events occurred as a result of the administration of parenteral buflomedil at a dose lower than the highest oral available dose.

The CHMP also noted that the 2nd enquiry performed in France in 2005 by both Pharmacovigilance and Control Poison Centres enquiry identified 38 cases of accidental overdoses with buflomedil solution for injection out of 188 cases of intentional or accidental overdoses with oral or IV route. These cases were associated with the 50 mg/5ml dosage in 10 cases and with the 400 mg infusion in 25 cases (unknown in 3 cases). Misuse or non compliance with the indication was found in 32 and 46 cases respectively for the solution for injection versus the oral form, with a higher frequency of non-compliance of the indication (39.5% vs. 6.1%) and misuse (65.8% vs. 25.7%), respectively in the solution for injection versus oral form. The nature of the misuse was known in 21 cases: excessive dosage (13 cases), too rapid infusion rate (6 cases), association of these two factors (1 case) or contra-indication (1 case). These effects were due to the lack of renal monitoring in patients with renal impairment in 16 cases (42%), with 2 patients with creatinine clearance < 40 ml/mn and 6 dialysis patients. Among these 38 patients, four patients died with a possible association of buflomedil solution for injection.

Clinical studies with buflomedil solution for injection

The CHMP noted a number of studies investigating the safety of injectable buflomedil formulations. Many of these studies used both the oral and the injectable formulations and the CHMP was of the same opinion as for the oral formulations, noting that the submitted studies were of low quality, small and used heterogeneous outcome measures and parameters. In addition, most studies were not randomised or controlled and some were open-label.

Discussion on Benefit-risk assessment of injectable formulations of buflomedil

With regards to safety of the injectable formulations of buflomedil, the CHMP noted that of the 24 reported cases (about 5% of all adverse drug reactions recorded in the MAH database), a majority (13 out of 24) were cases of accidental overdose (as a result of medication error / iatrogenic cause), where the patients were prescribed with higher doses than the daily recommended maximum therapeutic dose of injectable buflomedil (200 mg/day). Because these cases occurred in the hospital setting, the CHMP was of the view that these do not reflect intentional overdoses and concluded that the medically supervised administration of buflomedil, under the controlled settings described, does not seem to be sufficient to comply with the infusion rate and dosing recommendations, renal function monitoring in patients with renal impairment and contra-indication in severe renal impairment.

While acknowledging the iatrogenic nature of some of the cases, the CHMP noted that adverse events were reported in patients administered twice the daily dosage, which suggests that the risks are associated with overdoses of relatively small magnitudes. Buflomedil has a narrow therapeutic window and requires adjustment to renal function, which is known to be reduced and susceptible to rapidly deteriorate in patients with PAOD, as a result of the disease itself. The CHMP therefore considered that these cases provide supportive evidence of the cardiovascular and neurological risks of buflomedil.

According to the approved indication, the injection formulation of buflomedil is used to initiate PAOD therapy, to be followed by a switch to oral therapy. As a result, when addressing the risk-benefit of buflomedil under normal conditions for use, the CHMP assumed a switch to oral formulations and therefore considered that the risk/benefit of buflomedil injectable needs to be considered within the overall discussion of the risk-benefit of buflomedil.

2.2.5. Risk minimisation measures

Following the European PSUR assessment reviewed by Portugal, a number of measures were implemented in order to address the concerns expressed by France and Belgium, following the decision to withdraw the marketing authorisations for 300 mg tablet formulations. The MAH updated the Company Core Data Sheet (CCDS) with the changes proposed, deleting the various previously registered indications across the EU such as manifestations of cerebrovascular insufficiency; vertigo; tinnitus; mental deterioration; personality disorders; lability of memory and of capacity to concentrate; spatiotemporal disorientation; sequelae of cerebral apoplexy and of neurosurgical interventions; arterial circulatory insufficiency in limbs; Raynaud's syndrome and disease; Buerger's disease; erythrocyanosis and intermittent claudication. The indication was restricted to "*Symptomatic treatment of chronic peripheral vascular disease (stage 2) (intermittent claudication), in addition to other adequate medical treatment, including platelet antiaggregant therapy"*, bringing the indication section in line with that of the French SmPC. Significant changes were also made to the posology section to reflect the need to consider renal function. A contraindication in relation to severe renal insufficiency was added and the wording of the warning to prescribers regarding the need to measure renal function and the requirement of dosage adjustment in these situations was improved. In section 4.9, the wording was rearranged to indicate that serious symptoms in overdose occur rapidly. The MAH also committed to undertake a full benefit-risk assessment, which was completed in January 2010, following which further SmPC changes were proposed, including an additional warning regarding the monitoring of patients with a history of depression and/or drug overdose. The variations to implement these changes were submitted between December 2009 and April 2010. These are still ongoing in some countries and that to date, the SmPC changes have only been approved in four countries. Due to the significant changes in the Product Information it was also decided that a Direct Healthcare Professional Communication (DHPC) should be circulated.

The MAH stated that if the product is still being used to treat the previously indicated various disorders there is the possibility that the risk of overdose continues and cannot readily be reduced. It is also possible that for some of the indications previously registered, prescribing doctors who considered that buflomedil was an effective treatment may have continued to prescribe the product, despite the restriction of the indication. The MAH considered this to be a possible explanation for why the French Risk Minimisation Plan (RMP) has not been successful to date.

The MAH conducted a review of the demography of the observed serious reactions associated with overdose and death in patients taking buflomedil. The MAH was of the opinion that the 2010 benefit-risk assessment identified demographic findings among the affected patients which suggest that the implemented risk management measures have the potential to be effective and that the extent of the measures takes into account the difficulties which have been encountered in other member states,

although it is too early to assess the effectiveness of these measures as the Product Information changes have not been approved in all member states.

The CHMP noted that the MAH acknowledged in its written responses and during the oral explanation that the main risks associated with the use of buflomedil are serious cardiological and neurological adverse events. It is also believed that the narrow therapeutic margin is associated with an increased risk of fatality in the treatment population of intermittent claudication and that therapeutic overdoses with serious adverse effects could occur in patients with renal and hepatic insufficiency, where the dose is not adequately adjusted. The population of patients with PVD is likely to be aged over 40 years of age and these patients are also likely to have other underlying conditions associated with PAOD, such as diabetes, hypertension and high cholesterol levels. However, although renal or hepatic impairment is normally not likely to occur until a patient reaches 65 years, the risk factors for PVD could induce renal and hepatic impairment earlier. The main risk in this group of patients is therefore incidences of accidental overdoses due to non-adjustment of dosage.

The CHMP acknowledged that the harmonisation of the SmPC is still ongoing, following the European PSUR assessment but noted that the RMP proposed by Amdipharm in May 2010 was largely equivalent to the RMPs implemented in France in 1997 and 2006 respectively. The CHMP also noted the conclusion of the third pharmacovigilance enquiry conducted to assess the effectiveness of the risk minimisation measures, covering the period 2007 to 2009. The enquiry confirmed that despite the measures in place, buflomedil was often used in non authorised indications and that the posology was still often excessive or non-adapted to renal function. The enquiry identified 25 cases, an average of 8 cases per year compared to 21 cases per year in the previous enquiry (1998-2004) as well as a decrease in the number of notifications, probably related to a major decrease in buflomedil prescriptions (43% decrease of buflomedil sales over 3 years). However, definite or possible misuse was recorded in 15 cases out of 25, which is a two fold increase compared to the previous period. The adverse effects (AE) reported in these cases are compatible with an overdose in 9 cases and include 4 neurological and 5 cardiological AEs. For the 25 identified cases, the outcome was favourable in 20 cases, fatal in 2 cases and unknown for the remaining 3 cases. The two cases of death occurred in men aged 81 and 67 years. In the first case, the information was insufficient to conclude on a Voluntary Drug Intoxication (VDI) and in the second case, a case of overdose was considered probable (buflomedil blood concentration = 21.3 µg/ml) without any VDI mention in the record of the patient, who suffered from renal failure at the time of the prescription.

The CHMP also noted that the pharmacovigilance and toxicovigilance data showed no improvement of the safety profile of buflomedil despite the implementation of the RMP in France in 2006; instead an increase of the misuse (disregard of contra-indications or dosage recommendations) and the persistence of overdose were observed. The CHMP was therefore of the opinion that it is possible to conclude on the effectiveness of the proposed RMMs, despite the lack of implementation in all member states, due to their similarities to the ones implemented in France. The CHMP therefore concluded that the proposed RMM were inadequate and will not be sufficient to prevent the occurrence of serious adverse events with buflomedil.

Thalès observational drug utilisation study

The CHMP also noted the results of the Thalès observational drug utilisation study, conducted to assess the impact of the RMMs implemented in France. The study examined the prescription patterns of buflomedil for oral use, comparing a reference period of 6 months before the 2006 French evaluation (May to November 2006) with two 6-months evaluation periods following the implementation of the resulting risk minimisation measures and the circulation of a DHPC (January to July 2007 and July 2007 to January 2008). Data on treatment (dosage, posology, indication) and on patients (renal function, co-morbidities and co-medication) were collected. In total, over 300 000 patients were included (182 200 before the 2006 evaluation and 121 050 after). The study showed that about 30% of patients with renal failure still receive an excessive dose (35.7% of patient with severe renal impairment received an inappropriate dose (> 600mg/day) and 27.6% of patients with moderate renal failure received 600mg/day), although it was noted that this percentage had decreased from 75% prior to the DHPC. The CHMP was of the opinion that despite this reduction, the results raised serious concerns, as the percentage of patients at risk remained unacceptably high. In addition, the CHMP observed with concern that an initial assessment of renal function was only carried out in 20% of patients and that measurements of the creatinine clearance were only performed in 17% of patients, which shows that no renal function monitoring is taking place, despite the SmPC recommendations. The CHMP concluded that the impact of the implemented measures was very weak and that the

expected impact of the proposed measures was insufficient to adequately address the identified risks observed with buflomedil, under normal conditions of use.

Following an oral explanation held in July 2011, the MAH was requested to propose further risk minimisation measures and asked whether a restricted population could be identified. The MAH submitted a revised proposal including the following measures:

1) Product Information

The MAH proposed a number of additional revisions to the SmPC in addition to those already proposed, which again were generally similar to the ones introduced in France in 2006. Regarding the therapeutic indications, the MAH proposed to further restrict the population by narrowing the PAOD indication to patients with a reduced ankle-brachial index (ABI), whose claudication distance is within 200m and who are not indicated for surgery, resulting in the following indication:

*'Symptomatic treatment of peripheral arterial occlusive disease (Stage II) (intermittent claudication), in addition to other adequate medical treatment, including platelet anti-aggregant therapy. "Stage II" patients are unable to walk more than 200 metres without pain and without pain at rest***.**

"Loftyl is available for patients whose symptoms are related to peripheral arterial occlusive disease (PAOD) confirmed by measurement of the ankle-brachial index in whom surgery is not indicated.

Treated patients will frequently have advanced vascular disease and/or diabetes and the metabolic syndrome. Regular review of their symptoms and at least annual tests of renal function is required to adequately monitor the progress of their disease as well as to ensure the safe use of Loftyl (see Section 4.4 below)."

The MAH also proposed to add epilepsy as a contraindication, as seizure-type reactions have been observed in all datasets. Whilst there is no definitive evidence that buflomedil is seizurogenic, the MAH considered that this addition would be an appropriate measure to reduce the likelihood of these reports. In addition, the MAH proposed to insert a sentence in Section 4.5 on "the possibility of increasing the likelihood of seizure-type reactions when buflomedil is combined with other drugs that lower seizure thresholds". The MAH also proposed to revise the wording of the contraindication in severe renal impairment in order to improve compliance to prescribing in the event of renal insufficiency. Tachycardia and seizure-type activity would also be added to the undesirable effects section while haemofiltration would be added to Section 4.9 - Overdose as a method of reversing an intoxication with buflomedil.

In the package leaflet, the MAH proposed changes mainly related to informing patients about renal impairment and the need to consult their doctor in case of doubts or concerns. Patients would also be reminded to respect the indication and the contraindications, the need to monitor renal function and the adverse effects. A contact point for reporting ICSRs would be provided and a sentence instructing patients not to give their medicine to anyone else would be added.

The CHMP noted the MAH proposal to better define the indication but considered that these restrictions simply reflect modern good clinical practice. The similarity to the measures already in place in France means the new proposal adds very little in terms of restriction of the indication. Regarding the proposed special warnings in patients with advanced vascular disease and/or diabetes and metabolic syndrome, the CHMP agreed that this group of patients is at increased risk and that more frequent monitoring of their cardiovascular status and of their renal function is required on general clinical grounds. The CHMP considered that the fact that warnings are necessary is evidence of the high and serious toxicity of this drug.

The CHMP also noted that the MAH did not discuss the option of a further restricted population, such as in diabetes population. It is acknowledged that only one specific study (Diamantopoulos et al., 2001) assessed buflomedil in 40 diabetic patients.

2) Pack size reduction

Taking into account the French data suggesting that patients were likely to take only one pack of buflomedil in an intentional overdose, the MAH proposed to reduce the pack size proportionally to the tablet strengths, to minimise the consequences of an intentional overdose. The CHMP noted the MAH proposal, noting also that no proposal was made to withdraw the 300 mg tablets formulation, one of the strongest measures implemented in France in 2006 to try to reduce the number of deaths by voluntary overdoses.

3) Product Website

The MAH proposed to develop and launch a buflomedil-dedicated website in order to provide continuous information about the product, together with an interactive portal for the reporting of adverse drug reactions with the possibility of undertaking questionnaires (e.g. the post-authorisation safety study). The CHMP noted the proposal, which would be an additional tool for communication, but considered it unlikely to significantly improve the awareness of prescribers. A number of communication tools (such as DHPCs sent to healthcare professionals and pharmacists, information to emergency physicians describing acute symptoms in case of bufllomedil overdose) were already implemented in France and subsequent assessments have indicated that they were insufficient to modify the behaviour of the prescribers regarding compliance with indications and the renal monitoring.

4) Post-Authorisation Safety Study

The MAH proposed to undertake a post-authorisation safety study (PASS) upon reintroduction of the product, and in the light of understanding of previous studies to evaluate the impact of RMM, notably in France where the product was in widespread use. The MAH proposed a detailed design & methodology proposal. The main outcome would be suspected ADRs, clinical outcome / progress, change of treatment and treatment cessation. The study would include a cross-sectional, criterion-based Drug Utilisation and Safety Study (DUS). Centres for the study would be established across the EU. The CHMP stated that this would only be useful in the eventuality that all concerns regarding the risk associated with the use of buflomedil were resolved. A drug utilisation study would be requested, rather than the proposed PASS.

5) Additional pharmacovigilance activities

The MAH proposed to collect, evaluate and report spontaneous ADRs and ICSRs from the medical literature as per normal pharmacovigilance. The MAH also proposed to make arrangements to involve the Poison Control Centres (PCCs) and to establish communication channels in order for the MAH to be informed when case reports have been received. Regarding the PSUR frequency, the MAH proposed to revert to six-monthly PSURs for the first two years of the product being restored to the market, with a review of the timeframe after two years. The focus of the PSUR would relate to the ICSRs reported to the MAH, the implementation of the RMM with particular focus on neurological and cardiac adverse reactions and information on dosing in renally impaired patients. The MAH also proposed to make buflomedil available under a 'Black Triangle' scheme for enhanced reporting of all suspected ADRs (serious and non-serious), as foreseen in the new European PV legislation, to be implemented in July 2012. The CHMP noted the proposed additional pharmacovigilance activities but considered that while they may be useful to improve adverse events reporting and evaluation, signal detection by spontaneous reporting is no longer a priority, given that the risks associated with buflomedil are now identified and confirmed. Instead, the focus should be on minimising these identified risks and the CHMP considered the proposed measures inadequate to do so.

2.2.6. Overall summary on safety and on risk minimisation measures

With regards to safety, the CHMP concluded that the use of buflomedil is associated with a number of serious cardiological (mainly tachycardia, hypotension, ventricular rhythm disorders and cardiac arrest) and neurological (mainly convulsions, myoclonia and status epilepticus) adverse events, which occur under normal conditions of use, particularly in elderly patients, who are predominantly the patient population relevant to the approved indication. These risks are compounded by the fact that buflomedil is a substance with a narrow therapeutic index and that buflomedil treatment requires dose-adaptation to adjust for renal function. If dose-adaptation is not done correctly, this leads to serious and life-threatening toxicity. This is of particular concern as patients with peripheral vascular disease are inherently likely to experience decreased renal function due to the nature of their condition.

Regarding risk minimisation measures, the CHMP noted the MAH proposals but considered that these are unlikely to be sufficient to prevent the occurrence of serious cardiac and neurological adverse events under normal conditions of use nor reduce the well identified risks of accidental overdoses and non-compliance with renal function monitoring associated with the use of buflomedil to an acceptable level. The CHMP noted that according to the French experience (including the results of the Thalès study and the publication by Bruhat et al.), cases of non-compliance with the recommended dose, non-adjustment of dose in patients with renal impairment and lack of monitoring of renal function persist, resulting in cases of serious adverse events, which is unacceptable for a product for which the only benefit is a limited level of efficacy in the lower limb peripheral vascular disease indication. As the Risk Management Plan (RMP) proposed in the scope of this Article 107 procedure is equivalent to the French RMP implemented in 2006, the CHMP was therefore of the opinion that it is possible to conclude on the effectiveness of the proposed RMMs, despite the lack of implementation in all member states.

Having assessed the risk minimisation measures proposed by the MAH, the CHMP concluded that given the high risk with buflomedil, notably in patients with advanced vascular disease and/or diabetes and metabolic syndrome, in patients with impaired renal function and in elderly patients, no adequate or sufficient measures could be identified to reduce the risks associated with buflomedil to an acceptable level.

2.3. Discussion on efficacy

The MAH based its discussion on the efficacy of buflomedil in the treatment of intermittent claudication mainly on the relatively recent large placebo–controlled LIMB (Limbs International Medicinal Buflomedil) study, a published meta-analysis by Walker and MacHannaford (1995), published clinical investigations and a review of the haemodynamic and haemorheological properties of buflomedil.

2.3.1. LIMB study

LIMB (Limbs International Medicinal Buflomedil) was a double-blind, placebo-controlled study investigating the long-term effects of buflomedil in PAOD, enrolling more than 2,000 randomised patients with objectively-confirmed peripheral arterial occlusive disease (PAOD). The study was conducted to the standards of current Clinical Trials Guidelines for peripheral vascular disease. The MAH was of the opinion that the study demonstrated that patients with intermittent claudication benefit from treatment with buflomedil, as long-term treatment with buflomedil was associated with a statistically significant reduction in the primary endpoint of 24% compared with placebo.

However, the CHMP did not agree that the LIMB study allowed to conclude on a statistically significant reduction in the primary endpoint (combination of symptomatic deterioration of PAOD, amputations, MI, stroke, CV deaths) compared to placebo. The first analysis of the primary endpoint, conducted on the predefined date for the primary analysis, December 2003, did not demonstrate statistical significance (see Figure 1). Although there was a trend of a decrease in symptoms (symptomatic deterioration of PAOD, amputations), there was an increase in cardiovascular events (MI, stroke, CV deaths). In addition, the robustness of this study was considered limited.

	Buflomedil N =1037 N (%)	Placebo N = 1026 N (%)	P
Combined end-point (01/12/2003)	**90 (8.7)**	**114 (11.1)**	**0.0646**
Components of combined endpoint (1st critical event): - PAOD	**34 (37.8)**	48 (42.1)	
- Amputation	**6 (6.7)**	14 (12.3)	
- MI	10 (11.1)	**10 (8.8)**	
- Stroke	13 (14.4)	**11 (9.7)**	
- CV death	27 (30.0)	**31 (27.2)**	

Figure 1: LIMB study results, first analysis (01 December 2003)

Since the results of the first analysis of the primary endpoint did not reach statistical significance, a new analysis, not originally planned according to the study protocol, was performed taking into account events until 31/03/2004, when the blinding assessment was still ongoing. In this second analysis (see Figure 2), statistical significance was achieved for the combined endpoint. A significant reduction of the combined endpoint was found, however the incidence of the individual components non-fatal MI and stroke in the buflomedil group was again higher compared to the placebo group, which is of concern in a patient population at high risk of cardiovascular complications. Of note, 4 months after the primary analysis, the difference between the groups relies on only approximately 10 events (14 events of the primary endpoint occurred in the placebo group vs. 5 in the buflomedil group in this period).

	Buflomedil N =1043 N (%)	Placebo N = 1035 N (%)	P
Combined end-point (31/03/2004)	**95 (9.1)**	**128 (12.4)**	**0.0163**
Components of combined endpoint (1st critical event): - PAOD	36 (37.9)	**50 (39.1)**	
- Amputation	7 (7.3)	**15 (11.7)**	
- MI	**10 (10.5)**	11 (8.6)	
- Stroke	**13 (13.7)**	11 (8.6)	

- CV death	29 (30.5)	**41 (32)**	

Figure 2: LIMB study results, re-analysis (31 March 2004), submitted by Cephalon

To conclude, the CHMP did not consider the secondary ad-hoc analysis to be relevant from a methodological point of view due to bias and therefore concluded that it could not be used as reference for the analysis of the efficacy of buflomedil vs. placebo. Only the primary analysis, which did not demonstrate a statistically significant difference between buflomedil and placebo on the primary endpoint, can be considered relevant.

The CHMP also noted the recent LIMB-treadmill study, conducted in 200 patients as a sub-study of the earlier LIMB study. This study again demonstrated positive but moderate results compared to placebo on "pain-free walking distance" with an increase in 45 meters, and on "maximum walking distance" with an increase in 84 meters. The same limitations as for the original LIMB study were identified.

2.3.2. Published meta-analysis

Walker and MacHannaford (1995) performed a meta-analysis of randomised, double-blind, placebo-controlled studies on the effect of buflomedil on intermittent claudication, including ten studies conducted between 1980 and 1988 at 42 centres in seven countries (Germany, USA, UK, Austria, Greece, Sweden and South Africa). The analysis included a total of 744 patients who received double-blind treatment for at least four weeks, and in some studies up to six months. The MAH considered that the result of the meta-analysis demonstrated that buflomedil treatment has a significant positive therapeutic effect in intermittent claudication, based on improvement in exercise duration and that the average buflomedil-treated patient with intermittent claudication is likely to show greater improvement in walking distance than at least 60% of the patients treated with a blinded placebo.

The CHMP noted the Walker and MacHannaford meta-analysis but considered that only 2 studies (Trübestein, 1984 and Diamantopoulos, 1989) showed a statistical significant difference on "walking distance", while the other studies were not considered statistically significant. The CHMP also discussed the 2009 Cochrane review, from which most studies included in the Walker and MacHannaford meta-analysis were excluded, as they did not comply with modern quality criteria for randomised clinical trials. The Cochrane review also excluded the LIMB-treadmill study because of the many uncertainties with regard to performance, results and reporting. The only two studies included were the Trübestein (113 patients) and the Diamantopoulos (wholly diabetic population of 40 patients) studies. The improvement in pain-free walking distance in these studies were 75m and 81m, respectively, while the increase in "maximum walking distance" was 81m and 171m, respectively. The CHMP considered the methodology of these two studies to be of moderate quality.

2.3.3. Haemodynamic and haemorheological characteristics

The MAH stated that numerous pharmacodynamic and clinical investigations have demonstrated that buflomedil has favourable haemodynamic and haemorheological effects on the human microcirculation and can lead to an increase in oxygen uptake. Pharmacodynamic studies demonstrated that buflomedil increases the blood perfusion to lower extremities. Measured haemodynamic parameters including heart rate, and mean arterial blood pressure does not change significantly. Furthermore, buflomedil has several properties that may benefit patients with claudication, including vasoactive effects with enhanced blood cell deformability, and muscle cell metabolism. Inhibition of platelet aggregation has also been documented. A recent publication by *Tsantilas et al (2010)* demonstrated the beneficial effects of buflomedil on the peripheral microcirculation in patients with type 2 diabetes mellitus (T2DM) with overt micro- or macro-angiopathy. Patients showed a significant increase in volume ($P = 0.039$) and a trend for increase in both flow and velocity ($P=0.097$ for both parameters), in contrast with the control group, which showed a decrease in volume and flow ($P= 0.045$ and $P= 0.027$ respectively) whereas velocity did not change ($P=0.150$).

2.4. Overall summary of efficacy

Overall, the CHMP considered the clinical data submitted in support of the efficacy of buflomedil to be limited. The most recent trial data failed to demonstrate clinical significance. Consequently, while the demonstrated efficacy remains largely unchanged since the granting of the initial MA, the CHMP was of the opinion that the available evidence is not supportive of a significant clinical efficacy of buflomedil on cardiovascular events and on walking distance.

2.5. Overall benefit-risk assessment

With regards to safety, the CHMP concluded that the use of buflomedil is associated with a number of serious cardiological (mainly tachycardia, hypotension, ventricular rhythm disorders and cardiac arrest) and neurological (mainly convulsions, myoclonia and status epilepticus) adverse events, which occur under normal conditions of use, particularly in elderly patients, who are predominantly the patient population relevant to the approved indication. These risks are compounded by the fact that buflomedil is a substance with a narrow therapeutic index and that buflomedil treatment requires dose-adaptation to adjust for renal function. If dose-adaptation is not done correctly, this leads to serious and life-threatening toxicity. This is of particular concern as patients with peripheral vascular disease are inherently likely to experience decreased renal function due to the nature of their condition. The concerns regarding the rapid deterioration of renal function in these patients, requiring regular and frequent monitoring were also reiterated.

The CHMP assessed the impact of the risk minimisation measures previously implemented in France, consisting mainly of revisions to the SmPC and communication and noted the proposed extension of these measures to other member states. However, the CHMP considered that the risk minimisation measures proposed by the MAH are unlikely to reduce the serious cardiac and neurological adverse events associated with the use of buflomedil to a clinically acceptable level.

In addition, the CHMP noted the evidence of limited clinical efficacy of buflomedil, as demonstrated in recent clinical trials.

In conclusion, taking into account the serious cardiac and neurological adverse events associated with the use of buflomedil-containing medicinal products under normal conditions of use, the evidence of limited clinical efficacy which is insufficient to compensate for the risks associated with the use of buflomedil and the established concerns regarding the effectiveness of the risk minimisation measures, the CHMP considered that the risk-benefit balance of buflomedil-containing medicinal products is not positive under normal conditions of use.

3. Overall conclusion

The CHMP considered that a number of serious cardiac and neurological adverse events have been reported with the use of buflomedil under normal conditions of use, particularly in elderly patients. In this context, the narrow therapeutic index of buflomedil is of major concern, as patients with peripheral vascular disease treated with buflomedil are inherently likely to experience decreased renal function, due to the nature of their condition. The concerns regarding the rapid deterioration of renal function in these patients, requiring regular and frequent monitoring were also reiterated.

The CHMP also considered, based on the assessment of the impact of risk minimisation measures already implemented in some Member States and on the published literature, that the risk minimisation measures proposed by the MAH would not be able to adequately reduce the risks of serious adverse events to a clinically acceptable level.

Finally, regarding efficacy, the CHMP considered that buflomedil-containing medicinal products showed only limited clinical efficacy in the symptomatic treatment of chronic peripheral vascular disease.

The CHMP therefore concluded, in view of the available data, that the risks of serious cardiac and neurological adverse events associated with the use of buflomedil-containing medicinal products in the symptomatic treatment of chronic peripheral vascular disease, under normal conditions of use, outweigh the limited benefits.

The CHMP therefore considered that the risk-benefit balance of buflomedil-containing medicinal products is not positive under normal conditions of use, and therefore recommended the suspension of the Marketing Authorisations of buflomedil-containing medicinal products listed in Annex I of the Opinion in all concerned EU Member States. This opinion supersedes the opinion on temporary measures adopted on 4 July 2011.

For the lifting of the suspension the MAHs should provide convincing data to identify a population in which the benefits of buflomedil clearly outweigh its identified risks (see Annex III of the Opinion).

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.