Annex II

Scientific conclusions and grounds for the suspension of the marketing and use of the products presented by the EMA

Scientific conclusions

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

Buflomedil is an α1-, α2-adrenolytic agent with vasoactive and haemorheologic properties, improving 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 is currently approved in France in the treatment of "symptomatic peripheral arterial occlusive disease (PAOD Stage II) symptoms". The approved maximum daily dose in patients with normal renal function is 600 mg and 300 mg in patients with renal impairment. Usage of buflomedil according to these conditions is considered to be under normal conditions of use.

France previously conducted two pharmacovigilance and toxicovigilance investigations following reports 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. Following these enquiries, France took a number of national regulatory actions to minimise the risk of adverse events associated with buflomedil. In December 2010, a further French benefit-risk evaluation of buflomedil was carried out, following which the French National Competent Authority suspended all French Marketing Authorisations for buflomedil-containing products. As a result, a procedure under Article 107 of Directive 2001/83/EC, as amended was automatically initiated. The procedure started during the February 2011 CHMP meeting.

Discussion on safety

The CHMP noted a review of French Eudravigilance data analysing spontaneous reports associated with treatment with buflomedil, to identify cases where cardiac and neurological reactions occurred under normal therapeutic doses (i.e. maximum of 600 mg daily for the oral tablet formulation). The CHMP also considered a review of the individual case safety reports (ICSR) database conducted by the MAH, to identify cases of cardiological or neurological adverse events under normal conditions of use, 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. The CHMP also examined a review of all available individual case safety data related to buflomedil, conducted by the MAH, based on post-marketing safety data 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.

Serious cardiovascular and neurological adverse events under normal conditions of use

The EudraVigilance review identified 74 cases of adverse events associated with buflomedil, with a total of 35 cases recording cardiac adverse and 39 cases recording neurological adverse events. From these cases, a total of 12 cases were identified in which patients were treated within the maximum therapeutic range (i.e. up to 600 mg daily) of buflomedil. There were 6 cases of cardiovascular and 6 cases of neurological 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.

The MAH review of the ICSR database identified 33 cases involving the use of a maximum daily dose of 600 mg. From these, a total of 21 cases of neurological adverse events were retrieved. One patient experienced convulsions after taking 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, 32 cardiological adverse events were retrieved; the most frequent reactions were tachycardia, hypertension, flushing and hypotension.

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

The MAH review of the ICSR database identified 5 cases with known dosage occurring in elderly patients for whom dosage adjustment was required. The reported ADRs were mainly related to serious neurological and cardiovascular ADRs. In addition to these 5 cases, a further two cases related to renal impairment were identified, where the dose was unknown. In addition, review of all available individual case safety data related to buflomedil identified 28 cases of overdoses in elderly patients (over 65

years of age). In 70% of the cases, the dose of buflomedil received by the patients was inappropriate because of underlying renal failure. The CHMP also noted the two French pharmacovigilance enquiries covering the period 1998 to 2004 and 2006 to 2009. These reported 188 and 26 patients respectively who experienced AEs. The mean age was 70.2 and 71.6 years, respectively.

Safety of the injectable formulations of buflomedil

The CHMP also carried out a separate assessment of the safety of the parenteral formulations of buflomedil, which are used in the hospital setting for the treatment of severe chronic ischaemia of the lower limbs. 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. While acknowledging the iatrogenic nature of the reported cases, the CHMP considered that these cases provide supportive evidence of the cardiovascular and neurological risks of buflomedil, as adverse events were noted in patients administered twice the daily dosage, which suggests that the risks are associated with overdoses of relatively small magnitudes. 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.

Overall conclusions on 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.

Risk minimisation measures

Following a European PSUR assessment and a full benefit-risk assessment completed by the MAH in January 2010, the MAH proposed a number of measures to address the identified concerns. Various indications previously registered across the EU were deleted and the indication was restricted to the *Symptomatic treatment of chronic peripheral vascular disease (stage 2) (intermittent claudication)*, bringing it in line with the French SmPC. The need to consider renal function was also introduced. The CHMP acknowledged that variations to implement the European harmonisation of the SmPC are still ongoing in some countries but noted that the RMP proposed by Amdipharm in May 2010 was largely equivalent to the RMPs already implemented in France. The CHMP also noted the pharmacovigilance and toxicovigilance data which show no improvement of the safety profile of buflomedil despite the implementation of the RMP in France in 2006; instead, a two fold increase of misuse compared to the previous period was observed. The CHMP concluded that due to the similarities between the proposed RMMs and the ones implemented in France, it is possible to conclude on the effectiveness of the proposed RMMs, despite the lack of implementation in all member states and that these measures are inadequate 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, including 300 000 patients and conducted to assess the impact of the RMMs implemented in France on prescription patterns. The study compared a reference period of 6 months before the 2006 French evaluation with two 6-months evaluation periods following the implementation of the resulting RMMs and the circulation of a DHPC. The study showed that about 30% of patients with renal failure still receive an excessive dose, although it was noted that this had decreased from 75% prior to the DHPC. The CHMP was of the opinion that despite this reduction, 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 creatinine clearance were only performed in 17% of patients, 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.

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 CHMP noted the proposed additional revisions to the SmPC, restricting the population by further narrowing the PAOD indication and revising the wording of the contraindication in severe renal impairment in order to improve compliance to prescribing in the event of renal insufficiency. The CHMP also noted the MAH proposal to reduce the pack size, to minimise the consequences of an intentional overdose. The CHMP noted that the MAH did not propose to withdraw the 300 mg tablets formulation. The CHMP considered the proposal for a website dedicated to buflomedil to be unlikely to significantly improve the awareness of prescribers, as previous communication tools already implemented in France were insufficient to improve compliance with indications and renal monitoring. Regarding the proposed additional pharmacovigilance activities, the CHMP was of the opinion that signal detection is no longer a priority, given that the risks associated with buflomedil are now identified and confirmed. Having assessed the totality of the risk minimisation measures proposed by the MAH, the CHMP concluded that given the high risk with buflomedil, notably in patients with impaired renal function and in elderly patients, no measures could be identified to reduce the risks associated with buflomedil to an acceptable level.

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.

Discussion on efficacy

The CHMP noted the efficacy data submitted by the MAH, including the relatively recent large placebo–controlled LIMB (Limbs International Medicinal Buflomedil) study. Regarding the LIMB study, the results indicated a trend of a decrease in symptoms (symptomatic deterioration of PAOD, amputations) although there was an increase in cardiovascular events (MI, stroke, CV deaths). However, the CHMP noted that the analysis did not demonstrate statistical significance and that the results therefore did not allow to conclude on a statistically significant reduction in the combined primary endpoint compared to placebo. Overall, the CHMP considered the clinical data submitted in support of the efficacy of buflomedil to be limited. Consequently, while the 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.

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.

Grounds for the suspension of the Marketing Authorisations

Whereas

- The Committee 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.

- The Committee considered that 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 Committee raised concerns regarding the rapid deterioration of renal function in patients with peripheral vascular disease, requiring regular and frequent monitoring.

- The Committee 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 Marketing Authorisation Holder would not be able to adequately reduce the risks of serious adverse events to a clinically acceptable level.

- The Committee considered that buflomedil-containing medicinal products showed only limited clinical efficacy in the symptomatic treatment of chronic peripheral vascular disease.

- The Committee 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 Committee therefore considered that the risk-benefit balance of buflomedil-containing medicinal products is not positive under normal conditions of use.

Consequently, the CHMP recommended to the European Commission 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 Marketing Authorisation Holders should provide convincing data to identify a population in which the benefits of buflomedil clearly outweigh its identified risks (see Annex III).