Annex II

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Furosemide Vitabalans and associated names (see Annex I)

Furosemide is a loop diuretic which acts along the entire nephron with the exception of the distal exchange site. Furosemide has been authorised in the EU for more than 40 years.

The decentralised marketing authorisation application for Furosemide Vitabalans was made in accordance with Article 10(a) of Directive 2001/83/EC, which is a well-established use application. The application for Furosemide Vitabalans is therefore based on publicly available bibliographic data as it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognized efficacy and an acceptable level of safety.

The use of furosemide is wide in clinical practice and a number of published papers have been submitted in support of efficacy and safety during the decentralised procedure. The non-clinical overview referred to 29 publications up to year 2010 describing pharmacodynamics, general pharmacology, pharmacokinetic and toxicology studies. The clinical part of the dossier referred to 77 publications up to 2009 supporting the effect of furosemide in the treatment of oedema associated with congestive heart failure, cirrhosis of the liver and renal disease, including nephrotic syndrome and mild to moderate hypertension.

Part II.1.d) of Annex I of Directive 2001/83/EC states that “the non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product for which application for marketing authorisation has been made in spite of existing differences”.

During the decentralised procedure, Poland and Lithuania were of the opinion that bibliographic data on pharmacokinetics of furosemide, presented in the marketing authorisation dossier cannot be applied to Furosemide Vitabalans and should be regarded as not sufficient. The lack of data regarding the bioavailibity of the product could lead to unforeseeable changes in the pharmacodynamics response and therapeutic failure, as well as the occurrence of toxic effects.

The decentralised procedure was closed on day 210, with most of the Concerned Member States agreeing with the conclusions of the Reference Member State’s assessment report except Poland and Lithuania which raised a potential serious risk to public health (PSRPH). A referral was thus triggered at the CMD(h) and the applicant was asked to justify that the literature provided in support of this application was applicable to the product applied for and to demonstrate that the potentially lower or higher exposure to furosemide, when Furosemide Vitabalans is used compared to the exposure obtained following administration of the product used in the pivotal clinical studies described in the submitted literature, would not influence efficacy or safety. The major concern raised by Poland and Lithuania could not be solved during the CMD(h) referral and the issue was therefore referred to the CHMP.

In order to show the relevance of the bibliographic data used in support of the application for Furosemide Vitabalans, the applicant made reference to:

- Pharmaceutical data

The applicant's argument that traditional manufacturing methods as well as excipients widely used in tablet formulations would not cause potential lower or higher exposure to furosemide when Furosemide Vitabalans is used (compared to the exposure obtained following administration of other furosemide 40 mg tablets) cannot be considered as sufficient evidence to bridge the applied product and other furosemide described in the literature. Furthermore, the applicant provided a set of dissolution profiles comparing Furosemide Vitabalans with nine other furosemide 40 mg tablets. The results of this study showing that Furosemide Vitabalans had a similar dissolution profile as the other furosemide presented were not considered sufficient by the CHMP to demonstrate efficacy and safety of the product applied for. Indeed, furosemide is an active substance with low solubility and low permeability (BCS class IV) which does not support an extrapolation based on pharmaceutical data. Additional data would be needed to support the relevance of the bibliographic data to demonstrate the safety and efficacy of Furosemide Vitabalans. Furthermore, in vitro data cannot be sole proof that the clinical data from the submitted studies are applicable to Furosemide Vitabalans.

- Pharmacokinetics data

In response to the CHMP, the applicant further referred to published pharmacokinetics data presenting PK parameters of similar tablets formulations to Furosemide Vitabalans as well as different formulations (e.g. tablet 20mg). The results have shown that furosemide absorption is highly variable (AUC value varies from 793.8 to 3953 ng*h/ml, Cmax from 283,6 to 2636 ng/ml and ln Cmax values are almost a tenfold difference).

The CHMP considered that a wide range of pharmacokinetic values for different furosemide 40 mg products did not prove that the pharmacokinetic parameters of Furosemide Vitabalans will be within the same range. The pharmacokinetic parameters available in the literature are not sufficient to claim that Furosemide Vitabalans would have a similar bioavailability. Furthermore, given that furosemide is a highly variable compound, the submission of in vivo data was considered necessary in order to characterise the PK of the product together with justification that would allow establishing a bridge to the published data.

- Clinical data

To support the efficacy and safety of Furosemide Vitabalans, the applicant only referred to published studies. The study in support of the safety of furosemide (Dormans et al.[1]) presented by the applicant, was not considered as relevant by the CHMP, as furosemide in this study was used intravenously and Furosemide Vitabalans is intended to be used in oral administration as a 40mg tablet. The applicant's arguments saying that there is no correlation between the absorbed amount of furosemide and the diuresis, and that controlled-released and immediate-released formulation produce almost as much diuresis, was not considered as sufficient to prove the efficacy of Furosemide Vitabalans. Therefore, the literature data submitted by the applicant to support the safety and efficacy of furosemide did not provide sufficient evidence that the pharmacokinetics of Furosemide Vitabalans allow its safe and effective use in the same dosage and indications applied for.

Overall conclusion

On the basis of the bibliographic data submitted, taken together with the pharmaceutical data, the applicant failed to establish the relevance of these data to demonstrate safety and efficacy of Furosemide Vitabalans.

[1] Dormans et al. Diuretic efficacy of high dose furosemide pharmacokinetics and pharmacodynamics in health and disease - an update. J Pharmacokineti Biopharm, 1989 Feb;17(1):1-46

Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the October 2012 CHMP meeting, a request for a re-examination was received from the applicant Vitabalans Oy on 12 November 2012. The detailed grounds for re-examination were submitted on 21 December 2012. An ad-hoc expert meeting was convened on 13 February 2013 at the request of the applicant.

- Detailed grounds for re-examination submitted by the applicant

The applicant expressed its disagreement on some procedural aspects of the mutual recognition procedure, the CMDh procedure and the referral procedure under Article 29(4) of Directive 2001/83/EC.

However, it is noted that the CHMP is a scientific committee and that while it operates within the legal framework, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the CHMP, and therefore the re-examination of the referral procedure under Article 29(4) of Directive 2001/83/EC focussed only on the scientific points addressed in the grounds for re-examination.

The applicant expressed its disagreement with the CHMP opinion, focusing its scientific grounds on the following points, for which the applicant argued that clear justification or evidence had not been presented to explain:

- how the applied furosemide 40 mg product would cause a potential serious risk to public health
- why the safety and efficacy of the applied furosemide 40 mg product would be effectively different than in other furosemide 40 mg products
- why the pharmacokinetics parameters of the applied furosemide 40 mg product would be different than the pharmacokinetics parameters in other furosemide products described in literature and to what extent they would be expected to be different, and how this difference would cause a concrete potential serious risk to public health.

- CHMP conclusion on grounds for re-examination

As mentioned previously, Annex I of Directive 2001/83/EC states that the non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the products, for which application for a marketing authorisation has been made in spite of the existing differences.

A scientifically valid approach such as the demonstration of comparable pharmacokinetics was considered necessary to bridge Furosemide Vitabalans to a similar product.

In addition, it is also noted that according to the Guideline on the Definition of a Potential Serious Risk to Public Health, a potential serious risk to public health in relation to a particular medicinal product can be considered to exist if the data submitted to support therapeutic efficacy do not provide sound justification for the claims of efficacy and/or the clinical safety data does not provide adequate support for the conclusion that all potential safety issues have been appropriately and adequately addressed.

The CHMP is of the opinion that the applicant has not adequately demonstrated that the submitted published literature on furosemide was directly applicable to Furosemide Vitabalans.

The applicant's argument that traditional manufacturing methods as well as excipients widely used are sufficient to demonstrate the bridging between Furosemide Vitabalans and other furosemide products cannot be accepted. It is agreed that the manufacturing method is adequately described, however a robust manufacturing process is only a basis for further investigations on efficacy and safety of the applied product, and cannot be accepted as proof of equivalence to an authorised product.

The applicant also argued that dissolution behaviour together with evident pharmaceutical equivalence proves bridging between Furosemide Vitabalans and other authorised furosemide 40mg products. As discussed previously, *in vitro* data demonstrating similarity of dissolution profiles between Furosemide Vitabalans and other products containing furosemide do not prove that the bioavailability of these products would be similar, in particular, with a BCS class IV drug substance (low solubility, low permeability).

Based only on published literature data, it is not possible to conclude that the pharmacokinetic parameters of Furosemide Vitabalans would be within the same range than other furosemide 40 mg tablets referred to. It cannot be excluded that the bioavailability of the applied product may be lower or higher than the bioavailability of these products. Therefore, it not possible to conclude that the efficacy and safety of Furosemide Vitabalans will be the same as that of the products containing furosemide included in the submitted literature.

In addition, for highly variables drugs, as it is the product under application, it is considered necessary to investigate the pharmacokinetics behaviour in order to exclude any other potential product-related variations. Indeed, it cannot be excluded that the formulation of the applied product would behave differently in terms of pharmacokinetics compared to the products containing furosemide included in the submitted literature.

The dossier submitted by the applicant did not include any *in vivo* clinical data which could have demonstrated that pharmacokinetic profile of Furosemide Vitabalans is similar to the products containing furosemide included in the submitted literature. The CHMP is of the opinion that the comparability of the bioavailability between the applied product and a product included in the submitted literature should have been shown in order to claim the same indication. Therefore, the CHMP concluded that the efficacy of Furosemide Vitabalans has not been demonstrated in the applied indications, and this constitutes a potential serious risk to public health.

- Ad-hoc expert meeting

At the request of the applicant, an ad-hoc expert meeting was convened. The ad-hoc expert group considered that the published literature and the dissolution data provided by the applicant were not sufficient to prove the safety and efficacy of Furosemide Vitabalans. The group considered that manufacturing methods or dissolution data could not predict how the product would behave *in vivo*. It was considered necessary to have *in vivo* data especially with a drug exhibiting such wide range of pharmacokinetic values. One of the factors influencing furosemide's pharmacokinetic variability is precisely the absorption process which is dependent on the intrinsic properties of this substance/low solubility, low permeability associated with unknown formulation effects. The applicant's arguments that there is no correlation between the absorbed amount of furosemide and the diuresis, and that controlled-released and immediate-released formulation produce almost as much diuresis, were not considered as sufficient by the group to prove the safety and efficacy of Furosemide Vitabalans. Furthermore, the group considered that there is a safety concern to put a product on the market for such indication (heart failure) when the efficacy has not been demonstrated. Considering the foreseeable high variability of the product, the main risk with furosemide would be a lack of efficacy.

On the basis of the bibliographic data submitted, taken together with the pharmaceutical data, the applicant failed to establish the relevance of these data to demonstrate safety and efficacy of Furosemide Vitabalans.

Grounds for refusal

On the basis of the bibliographic data submitted, taken together with additional pharmaceutical documentation, the applicant failed to establish the relevance of these data to demonstrate the safety and efficacy of Furosemide Vitabalans and associated names.

Whereas

- The Committee considered the notification of the referral triggered by Estonia under Article 29(4) of Directive 2001/83/EC. Poland and Lithuania considered that the granting of the marketing authorisation constitutes a potential serious risk to public health.
- It has not been sufficiently demonstrated by the applicant that a potentially lower or higher exposure to furosemide would not influence the efficacy or safety.
- The provided data do not show that Furosemide Vitabalans is similar to the products described in the submitted literature. In view of this lack of evidence the Committee found merit on the concerns raised by the Member States on the potential serious risk to public health.

The CHMP has recommended the refusal of the granting of the marketing authorisation for Furosemide Vitabalans and associated names (see Annex I).