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Assessment report for Furosemide Vitabalans

Referral under Article 29(4) of Directive 2001/83/EC

INN of the active substance: Furosemide

Procedure no: EMEA/H/A-29/1334

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. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Vitabalans Oy submitted applications for decentralised procedure of Furosemide Vitabalans and associated names, 40 mg tablets on 25 February 2011.

The applications were submitted to the reference Member State (RMS): Estonia and the concerned Member States (CMS): Czech Republic, Denmark, Finland, Hungary, Latvia, Lithuania, Norway, Poland, Sweden, Slovenia and Slovak Republic.

The Decentralised procedure EE/H/0171/001/DC started on 1 April 2011.

On day 210, Poland's major issues on safety and efficacy, remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, by Estonia on 20 February 2012. The CMD(h) 60 day procedure was initiated on 27 February 2012.

Day 60 of the CMD(h) procedure was on 26 April 2012 and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC, to the CHMP was made by Estonia on 27 April 2012. Poland raised public health objections on the grounds that bibliographic data on pharmacokinetics of furosemide, presented in the dossier cannot be applied to the product due to lack of bridging data and should be regarded as not sufficient to support this application. It is not possible to determine the bioavailability of the product and this may lead to unforeseeable changes in the pharmacodynamic response and therapeutic failure, as well as the occurrence of toxic effects. This position was supported by Lithuania.

2. Scientific discussion during the referral procedure

2.1. Introduction

Furosemide is a loop diuretic which acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henle with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex. The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium chloride from the nephron is reduced and hypotonic or isotonic urine produced. Adverse effects unrelated to the diuretic efficacy are rare, and most adverse effects are due to abnormalities of fluid and electrolyte balance, and occur at high doses and/or prolonged use.

The proposed indications for Furosemide Vitabalans are: for the treatment of oedema associated with congestive heart failure, cirrhosis of the liver and renal disease, including nephrotic syndrome (in case of treatment failure with or intolerance to corticosteroids and in patients with nephritic syndrome, therapy of the underlying disorder has priority) and for mild to moderate hypertension.

Furosemide Vitabalans 40 mg tablets is a conventional compressed immediate release tablet with the active substance furosemide approved in the European Union for more than 40 years.

The decentralised marketing authorisation application presented for the medicinal product Furosemide Vitabalans 40 mg tablets is a well-established use (WEU) application according to Article 10a of Directive 2001/83/EC. 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 literuature (information available in the public domain) if it can be demonstrated that the active substance of a medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and acceptable level of safety.

During the decentralised procedure, Poland expressed 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). 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.

2.2. Critical evaluation

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.

The publications on the clinical pharmacokinetic of furosemide concluded that furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastro-intestinal tract. Furosemide is fairly rapidly absorbed from the gastrointestinal tract on oral administration but its absorption is variable. Its bioavailability is about 60 to 70%. The elimination half-life of furosemide is up to about 2 hours. The peak plasma concentration of furosemide is reached at 1 to 2 hours and the duration of action is about 4 to 6 hours.

However, the data submitted were not considered as sufficient by the CHMP, and the applicant was asked to further justify that the literature provided in support of the application is applicable to Furosemide Vitabalans. The literature should demonstrate that the potentially lower of higher exposure to furosemide, when Furosemide Vitabalans is used, compared to the exposure obtained following administration of the product used in the pivotal studies described in the submitted literature, would not influence efficacy or safety.

Furthermore, 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".

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

- **Pharmaceutical data**

Furosemide Vitabalans is a direct compressed tablet manufactured with traditional and simple tablet manufacturing method. The applicant has presented a comparison of excipients used in different immediate-release furosemide tablets which showed that the excipients in Furosemide Vitabalans' formulation are also used in other authorised furosemide 40 mg tablets products. Specification requirement for furosemide content in one tablet is 40 ± 5%, which means that after administration of one tablet the lowest possible exposure to furosemide is 38 mg and the highest possible exposure is 42 mg. Batch analysis has been performed on three batches of Furosemide Vitabalans and the results showed that the finished product meets the specifications proposed.

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 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 dissolution results showed that all studied furosemide 40 mg tablets have released at least 85% of furosemide after dissolution period of 15 minutes at pH 5.8. 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. Therefore, in vitro data cannot be sole proof that the clinical data from the submitted studies are applicable to Furosemide Vitabalans. This view is also supported by the article of Granero et al.[1].

- **Pharmacokinetics data**

In response to the CHMP, the applicant has referred to literature data showing that the pharmacokinetics of furosemide are linear over the oral dosage range of 20-80 mg/day.

Published pharmacokinetics studies comparing PK parameters of similar tablets formulations to Furosemide Vitabalans as well as different formulations (i.e. tablet 20 mg, retarded capsule 40 mg, sublingual 20 mg and i.v. 20 mg) have shown that the absorption of furosemide is highly variable. The individual results calculated using the standard deviation showed that after ingesting a 40 mg tablet of furosemide, 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 standard deviation in all results was significant and emphasized the very high variability of furosemide compound, which has been reported to be from 20 to 84%. In accordance with these results, it is acknowledged by the applicant that the very high intra- and inter-individual variability of furosemide compound may need to be taken into account with medical supervision during the treatment. The applicant also highlighted that furosemide has always been dosed by clinicians according to the patient's response.

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

[1] Granero GE, Longhi MR, Mora MJ et al. *Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Furosemide.* Journal of Pharmaceutical Sciences, 2010; 99(6):2544-56.

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.

On 18 October 2012 in a letter addressed to the EMA, the applicant has committed to carry out in vivo clinical study in order to study and compare the pharmacokinetic parameters of Furosemide Vitabalans 40 mg tablet in urea to the originator product. In the absence of any precise timeframe for the conduct of this study the CHMP did not consider that proposal as acceptable in the context of this referral procedure.

- **Clinical aspects**

To support the efficacy and safety of Furosemide Vitabalans, the applicant only referred to published studies.

To support the safety of the product, the applicant referred to a study (Dormans et al.)[2] where furosemide is used intravenously in 20 patients with severe heart failure. The results showed that 5 patients had reported adverse events and that in overall furosemide was well tolerated and safe. However, these results were 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 40 mg tablet.

Furthermore, 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 safety and 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.

2.3. 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.

[2] 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

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.

2.4. Risk management plan

The CHMP did not require the applicant to submit a risk management plan.

2.5. Recommendation

The use of traditional manufacturing methods as well as excipients widely used in tablet formulations cannot be considered as an adequate bridge between the product applied for and the products described in the literature. It has not been established that the literature data provided is relevant to Furosemide Vitabalans 40mg tablets, even taking into account the similarity of the dissolution profiles. In vivo data are necessary to characterise the pharmacokinetics of the product, in particular for such highly variable products.

In view of the above, the CHMP is of the opinion that the data provided by the applicant are not sufficient to support the safety and efficacy of the product applied for in the sought indications.

2.6. Conclusions and benefit risk assessment

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.

Based on the rapporteur's and co-rapporteur's assessment reports and scientific discussion within the Committee:

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.