Annex II

Scientific conclusions and grounds for the addition of three manufacturing sites to the marketing authorisations and amendment of the summaries of product characteristics and package leaflets presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation on the inclusion of additional sites into the existing licenses of dialysis solutions (Dianeal, Extraneal and Nutrineal) produced by Baxter group of companies and associated companies (see Annex I)

An article 31 referral procedure of Directive 2001/83/EC, as amended was initiated by the European Commission (EC) following reports of out-of-specifications results for endotoxins in dialysis solutions produced at Castlebar by Baxter group of companies and associated companies. In particular, the peritoneal dialysis (PD) Dianeal, Extraneal and Nutrineal were affected by this procedure. Taking into account the crucial nature of these medicinal products, unaffected batches of PD solutions had to be made available to patients across the EU in the shortest possible timeframe, and thus alternatives were sought. In view of severe supply limitations for Dianeal, Extraneal and Nutrineal and the risk of switching patients to alternative PD solutions or therapies, the CHMP considered that the use of comparable products produced by Baxter at alternative manufacturing sites outside the EEA (European Economic Area) should be prioritised. These dialysis solutions were thus imported from Canada, Singapore, Turkey and USA. To meet supply demands, the unprecedented importation of PD solutions from Canada, Turkey and USA increased. The Singaporean manufacturing plant was only used once and no longer considered as an alternative.

Considering the likelihood of prolonged use of large quantities of unlicensed (imported) PD solutions on the EU market, and in order to ensure continued supply of licensed medicinal products to the EU, the necessary data packages to support the inclusion of additional manufacturing sites were expedited within the ongoing article 31 referral procedure.
The available data to support inclusion of sites from which products are currently being imported (Canada, Turkey and USA) into the existing PD solutions marketing authorisations were submitted. The necessary data packages to support the inclusion of one more additional manufacturing site located in Europe (Poland) which is expected to become fully operational soon, was also expedited. In light of the current uncertainty over the root cause and the future re-instatement of supply from Castlebar, the addition of manufacturing sites to the marketing authorisations aimed at mitigating future supply problems arising for PD solutions in Europe, ensuring that sufficient PD solutions are available.

The CHMP reviewed all the data available for each of the four sites concerned. At this stage of the article 31 review procedure, sufficient data is available to recommend the variation to the marketing authorisations consisting in the inclusion of Canada, Poland and Turkey as additional manufacturing sites, as no major quality issues were identified at these sites. Presently, the information available on the USA site is insufficient to conclude on its addition, pending the outcome of a recent inspection carried out at this site. Furthermore, the opinion on the Castlebar site cannot be finalised at this stage as issues remained for resolution by the marketing authorisation holder.

The review of the issues identified at Castlebar, with the interruption of supply from this site, led to the need to authorise additional manufacturing sites to ensure supply of PD solutions in Europe. Whilst all data to finalise the ongoing article 31 is not available, a stepwise approach is followed for the assessment, resulting in subsequent opinions being adopted by the CHMP.

Therefore, without prejudice to the ongoing article 31 procedure, the CHMP considers that sufficient information is available to issue a first opinion for this Article 31 procedure recommending the addition of Canada, Poland and Turkey manufacturing sites to the existing PD solutions' marketing authorisations, subject to conditions set out in the Annex IV. Overall, the following should be taken into account:

- All drug substances should be supported by active substance master files or appropriate data and comply with Ph Eur requirements.

- All starting materials (including excipients) should be subject to satisfactory routine control of microbial contamination and, unless justified, endotoxin testing.

- Water for injections, and other excipients, should fully comply with Ph Eur monograph requirements, where applicable.

- The current minimum standards for critical process parameters and limits e.g. for terminal sterilisation should be reviewed and improved, in compliance with process capabilities and best practice. Terminal sterilisation has to be expressed as a minimum exposure time to a minimum

temperature as per Ph. Eur. and should be harmonised at all involved sites. Consequently bioburden specifications of the filled containers should also be harmonised.
The sterilisation process should be re-validated using biological indicators as per Ph. Eur..

Standard QP release should apply for all products released under the terms of EU marketing authorisations; in particular the QPs must be satisfied that the active substances are manufactured in accordance with EU GMP requirements.

Pending conclusion of the ongoing Article 31, it is expected that the MAH implements in all its sites the outcome of lessons learned from the findings at Castlebar, to ensure a safe product supply. The introduction of a more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing and the re-submission of the full description of the manufacturing processes for all sites together with its critical review should thus be undertaken. Additional measures may be requested subsequently for these sites, but pending conclusion of the ongoing article 31 these cannot be identified.

The CHMP considers of extreme importance to retain coordination of the review of the conditions presently identified for the sites in Canada, Poland and Turkey. A harmonised European approach to supply has been in place since identification of the concern at Castlebar and the article 31 procedure remains ongoing pending resolution of the outstanding issues. The present opinion is the first of a series of entwined opinions, which may result subsequently in additional measures being requested for the sites subject of the current opinion. The coordinated review of the conditions by the CHMP will enable the appropriate harmonious adjustments with minimum impact on supply of PD solutions to the EU market.

Grounds for the addition of three manufacturing sites to the marketing authorisations and amendment of the summaries of product characteristics and package leaflets

Whereas

- The CHMP considered the referral under Article 31 of Directive 2001/83/EC, as amended, for dialysis solutions produced at Castlebar by Baxter group of companies and associated companies.
- The review of the issues identified at Castlebar is ongoing, and peritoneal dialysis solutions are not being released from this manufacturing plant which is the main marketing authorisation holder's supplier in Europe.
- Unaffected batches of peritoneal dialysis solutions needed to be made available to patients across the EU in the shortest possible timeframe, thus alternative PD solutions produced by Baxter at alternative manufacturing sites outside the EEA (European Economic Area) were prioritised.
- The CHMP considers that sufficient quality data is available to recommend the inclusion of manufacturing sites located in Canada, Poland and Turkey into the existing marketing authorisations for peritoneal dialysis solutions.

the CHMP recommends the variation to the terms of the marketing authorisations concerning the addition of three manufacturing sites (Canada, Turkey and Poland) and for which the relevant amendments to sections of the summaries of product characteristics and package leaflets are set out in Annex III for dialysis solutions produced by Baxter group of companies and associated companies (see Annex I). The conditions affecting the marketing authorisations are set out in Annex IV of the opinion.