Annex II

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of dialysis solutions from Baxter group of companies and associated companies produced at Castlebar (see Annex I)

An article 31 referral procedure of Directive 2001/83/EC was initiated by the European Commission (EC) following receipt of information from Baxter indicating that their manufacturing problem related to out-of-specifications results for endotoxins in dialysis solutions produced at Castlebar was not resolved and the root cause had not been identified. Products manufactured at the affected lines in Castlebar included peritoneal dialysis (PD) solutions Dianeal, Extraneal and Nutrineal; and Monosol and 0.9% sodium chloride for haemodialysis.

Taking into account the crucial nature of these medicinal products, and the need for unaffected batches of dialysis solutions to be made available to patients across the EU in the shortest possible timeframe, 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, as these products were assessed to be therapeutically equivalent to the EU products, and there was sufficient reassurance regarding their quality. 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. Monosol and 0.9% sodium chloride for haemodialysis solutions were promptly recalled from the market as alternatives were available.

Considering the likelihood of prolonged use of large quantities of imported PD solutions on the EU market, and in order to ensure continued supply of licensed medicinal products to the European Union, the necessary data packages to support the inclusion of additional manufacturing sites were expedited within the article 31 referral procedure. Whilst all data to finalise the article 31 was not available, a stepwise approach was followed for the assessment, resulting in subsequent opinions being adopted by the CHMP.
Two initial opinions were issued. The first on the inclusion of the sites located in Canada, Poland and Turkey as additional manufacturing sites to the marketing authorisations of the respective peritoneal dialysis solutions was issued by the Committee in April 2011, and the corresponding decision from the Commission was issued on 12 May 2011. A second opinion was then issued in May 2011 to recommend the inclusion of the site located in USA as an additional manufacturing site. The corresponding decision from the Commission was issued on 13 July 2011.

The CHMP is now in a position to issue a third and final opinion on the article 31 review procedure focusing on the issues at the Castelbar site.

Further to the out-of-specification endotoxin results observed in batches manufactured in one area of the Castlebar manufacturing site, an investigation into the root cause was undertaken. Although protein/biofilm were not found upon dismantling the line, Gram positive and Gram negative microorganisms were identified. Overall, a combination of factors may have played a role in the findings, such as inadequately designed equipment, mechanical failure of equipment (cracks having been detected in some tanks used in the affected lines), methods of microbial monitoring not applied routinely and not state of the art, including outdated methods for monitoring endotoxins, and an inadequate cleaning and sanitisation regimen.
Enhancements of the affected line were proposed in order to prevent the occurrence of future biofilm/microbial contamination problems. New re-designed equipment was installed with the intention of minimising areas where pooling of water/solutions could occur. Modern rapid microbial methods should be applied on site to raw materials, excipients and finished product, to reduce variability, improve turn around time and improve the quality of information. A more sensitive method for endotoxin testing should be implemented and its limit of detection will be tightened for both finished product and excipients. This should allow early detection of low levels of endotoxin and trend analysis which should provide an early safety warning. Cleaning/sanitisation procedures were also reviewed and installation and qualification of all of these enhancements should be reviewed by the supervisory authority through inspections before any solutions produced in these lines can be released to the market. Once this process is completed, the marketing authorisation holder (MAH) should submit variations to the national competent authorities to update the marketing authorisations of the affected dialysis solutions. A 12 month monitoring should also be undertaken upon qualification. This will be an intensive period of monitoring to establish that the site is performing to acceptable standards. All

changes to processes, frequencies or limits resulting from the evaluation should also be submitted to the national competent authorities through appropriate regulatory procedures.

On the basis of the proposed measures, the CHMP was reassured that corrective actions are being implemented and will be subject of further monitoring. The CHMP requests that the inspection of the Castlebar site be performed by the end of December 2011 and that the outcome of the inspection be provided to national competent authorities.

Considering the global implications of the findings at Castlebar, and proposed improvements at this manufacturing site, global corrective and preventive actions (CAPA) should be drawn up and used to audit other sites producing dialysis solutions, including those authorised in the framework of this procedure at the time of the first and second opinions. The MAH proposed a change management plan on the development of the CAPA which was agreed by the CHMP. The outcome of global CAPA will be provided to the national competent authorities and any changes considered necessary should be addressed through the appropriate change management protocols and subsequent regulatory procedures at a national level, as applicable.

In addition to the programme of quality improvement, future assured supply steps were developed. A plan for maintenance of existing manufacturing sites, registration of additional sites located in Italy and the UK, expansion of different sites to increase its capacity and contingency for sufficient alternative providers/stocks for raw materials was agreed. The MAH should submit variations to increase the diversity of supply, to national competent authorities in line with agreed timelines.

During the article 31, several measures were put in place in order to monitor the risk of developing aseptic peritonitis, identified as the primary risk following the use of dialysis solutions manufactured at the affected manufacturing lines in Castlebar. Weekly reports of adverse drug reactions and batch signal data was undertaken, and a batch recall performed in case a signal arose with a particular batch. This heightened pharmacovigilance was applied to products from alternative sites supplying Europe. It was noted that the risk for aseptic peritonitis increased if a patient was using one or several affected bags of batch/batches containing increased levels of endotoxin. Further to the replacement of the product from Castlebar, mostly completed in April 2011, a decline in the number of aseptic peritonitis cases reported was observed. Following continued review until September 2011, the CHMP now considers that weekly reports can cease, and the MAH should promptly inform the appropriate national competent authorities of any data suggestive of a signal with the dialysis solutions on the market.

The product information for dialysis solutions includes the risk of peritonitis. As an additional measure, a consolidated risk management plan (RMP) specific for the re-launch of dialysis solutions manufactured at the Castlebar lines affected by the endotoxin issue has been submitted. Weekly reports will be reintroduced for eight weeks followed by four monthly reports once solutions from the Castlebar plant using the new manufacturing lines are produced. Other enhanced pharmacovigilance activities include the clinical audit that will collect data on the number of peritonitis events in the EU and an observational study to assess the severity of peritonitis episodes (including fatal outcomes) and the impact on longer term clinical outcome. Additional risk minimisation activities focus on reporting of batch numbers, communication via a direct healthcare professional communication and an adverse event questionnaire in addition to quality risk minimisation activities. The CHMP agreed with the proposed studies. The MAH should submit the relevant data to national competent authorities for review, in line with the agreed milestones for evaluation and reporting as described in the RMP.

For completeness, the CHMP considered that a pharmacovigilance inspection should be carried out. Focus should be given to the timeliness of communication of safety signals to healthcare professionals and competent authorities, and the accuracy and consistency of the systems in place to collect safety information and provide it to the regulatory networks.

In view of the above, the Committee considers that the benefit risk balance of dialysis solutions from Baxter produced at Castlebar under review through this procedure, is positive under normal conditions of use and therefore recommends the variation to the terms of the marketing authorisations, subject to conditions set out in the Annex III.

Grounds for variation of the marketing authorisations

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC, for dialysis solutions from Baxter group of companies and associated companies produced at Castlebar (see annex I).

- The Committee considered all data submitted by the MAH, in writing and at oral explanations, including the overall root cause investigation report, and concludes that the MAH has performed a comprehensive investigation of the root cause leading to the out-of-specifications for endotoxins in dialysis solutions produced at particular lines of manufacture in Castlebar. The investigation supports that a combination of factors have contributed to the findings.

- The Committee considers that critical enhancements have been introduced, including the re-design of the affected lines, introduction of modern rapid microbial methods on site to raw materials, excipients and finished product, and a more sensitive method for endotoxin testing, with tightened limit of detection for both finished product and excipients. Cleaning/sanitisation procedures were also reviewed and installation and qualification of all of these enhancements should be reviewed by the supervisory authority through inspection of the Castlebar site. Dialysis solutions produced at the affected lines are not being released onto the market pending the outcome of this inspection. The MAH should also submit the appropriate variations to the national competent authorities to update the marketing authorisations affected dialysis solutions, in accordance with agreed change management plans.

- The Committee considers that the establishment of a 12 month monitoring period, upon qualification of the Castlebar plant by the IMB, is appropriate. This period of intense monitoring will bring further reassurance that the site is performing to acceptable standards. If changes to processes, frequencies or limits emerge from this period of monitoring, the MAH should submit the appropriate variations to the national competent authorities to update the marketing authorisations of the affected dialysis solutions, as applicable.

- The Committee agreed with the change management plan for development of the global corrective and preventive actions (CAPA) at Castlebar. The MAH should use this to prevent endotoxin contamination at other sites producing dialysis solutions for Europe, and apply all lessons learned accordingly. Member states should ensure that measures are implemented in accordance with global CAPA during inspections of the sites located under their territories. Care should be taken to ensure consistency.

- The Committee considers that the future supply programme submitted by the MAH adequate. The MAH's plan for maintenance of existing manufacturing sites, registration of additional sites and expansion of production capacity of others is appropriate. The contingency plan for sufficient/alternative providers/stocks for raw materials was agreed. The MAH should update the existing marketing authorisations and submit variations to national competent authorities in accordance with the agreed change management plan.

- The Committee requires the MAH to perform the epidemiological studies agreed, the clinical audit and observational study, and other measures as detailed in the risk management plan.

- Finally, the Committee considers that a pharmacovigilance inspection should be carried out for completeness and to ensure that communication of safety signals to healthcare professionals and competent authorities is adequate, and the systems in place to collect safety information and provide it to the regulatory networks are accurately and consistently applied.

In view of the above, the Committee considers that the benefit risk balance of dialysis solutions from Baxter group of companies and associated companies produced at Castlebar (see Annex I) is positive and therefore recommends the variation to the terms of the marketing authorisations, subject to the conditions set out in annex III.