Annex II

Scientific conclusions and grounds for maintenance of the marketing authorisations or the variation to the terms of the marketing authorisations, as relevant

Scientific conclusions

Overall summary of the scientific evaluation of polymyxin-based products (see Annex A and Annex I)

The emergence of multi-drug resistant Gram-negative bacteria that cause nosocomial infections is a growing problem worldwide. Limited therapeutic options have led to an increased clinical use of colistin, a polymyxin antibiotic developed over 50 years ago and which has retained activity against a number of multi-drug resistant pathogens. This is possibly because of its limited parenteral use, due to the existence of safer, less neurotoxic and nephrotoxic therapeutic options. As a consequence, the existing preclinical and clinical pharmacokinetic (PK) and pharmacodynamic (PD) information is limited, the product information has not been significantly updated over the years and the dosage regimens in use today are not based upon robust PK/PD data. Indeed, recent clinical experience and the medical literature point to the urgent need to update the product information, in particular the indications, the dosage recommendations and the PK/PD information, as highlighted by recent reports of suboptimal efficacy and the emergence of colistin resistance, in particular when used as monotherapy. In addition, differences across the world in the expression of the strength and dose of colistin products may result in medication errors and put patients at risk.

Polymyxins are currently listed among the critically important antimicrobials and in view of the importance of ensuring the availability of efficacious and safe antibiotics in order to efficiently respond to the threat posed by the spread of antimicrobial resistance, the European Commission initiated a procedure under Article 31 of Directive 2001/83/EC on 16 September 2013, requesting the CHMP to give its opinion on the benefit-risk of polymyxin-based products and on the need for regulatory measures.

The CHMP decided that the medical need was greatest for high dose products for parenteral and inhalation use and that the scope of the review should be limited to these medicinal products. The scope of the procedure includes nationally-authorised medicinal products and a centrally-authorised medicinal product, Colobreathe (dry powder for inhalation), authorised in February 2012. In its assessment, the CHMP reviewed all available data, including submissions by marketing authorisation holders during the procedure and consulted the Pharmacokinetics Working Party and the Infectious Disease Working Party.

Polymyxins are a group of naturally occurring antibiotics produced by the bacterium *Paenibacillus polymyxa*. Only polymyxin E (referred to as colistin) is approved for clinical use in the EU. Two forms of colistin are used clinically: colistin sulphate and its microbiologically inactive prodrug, colistimethate sodium (CMS). Colistin has a relatively high level of toxicity associated with parenteral administration and CMS was therefore developed for parenteral and inhalation use. CMS for parenteral use is indicated for the treatment of serious infections caused by Gram-negative pathogens and CMS for inhalation use is indicated for the management of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis.

Having reviewed all available data, the CHMP considered that CMS and colistin represent a crucial therapeutic option in the armamentarium available to prescribers in the context of the treatment of infections caused by multi-drug resistant Gram-negative pathogens. A large number of PK/PD studies were reviewed together with data from clinical experience and the CHMP considered the available data to be sufficient to support revisions of the indication for both parenteral and inhalation use products, in line with clinical experience and current therapeutic guidelines. It was agreed that colistin can be used without age restrictions, but only for the treatment of serious infections. A key concern is to maintain the efficacy of colistin against multi-drug resistant pathogens and to avoid the selection of resistance arising from monotherapy and the CHMP therefore agreed recommendations for the co-administration of parenteral colistin with other antibiotics. The posology and method of administration section was also revised in its entirety, for all patient subpopulations, in order to define the optimal treatment regimens for achieving plasma concentrations above the critical minimal inhibitory concentrations. In particular, the CHMP considered that a loading dose should be administered, to ensure plasma concentrations above the minimum inhibitory concentration from the very first administration. However, data was extremely limited in certain patient populations and as a result, no firm recommendations could be made for patients with renal impairment, on renal replacement therapy or with hepatic impairment. Data was also particularly limited for paediatric patients.

The CHMP reviewed the optimal way of expressing the strength and dose of polymyxin-containing products and was of the opinion that given the established use of international units (IU) in EU clinical practice and in the European and British Pharmacopoeia, the EU product information for CMS should

continue to be expressed in IU. However, the CHMP introduced a dose content conversion table between CMS expressed in IU, CMS expressed in mg and CBA expressed in mg, to raise awareness of the different ways of expressing the strength and dose and to help prescribers who obtain additional information from the literature.

The CHMP also reviewed the data on adverse events observed with the use of colistin and agreed that the use of colistin for parenteral use is associated with nephrotoxicity and neurotoxicity but considered that these risks must be balanced against the risk of the underlying disease and the high mortality from the treated conditions and that they can be satisfactorily mitigated by statements in the SmPC. Finally, extensive revisions were made to reflect current pharmacokinetic and pharmacodynamic data, including an update of the EUCAST breakpoints and the list of susceptible species. Corresponding changes were made to the package leaflets.

In conclusion, the CHMP is of the opinion that the benefit-risk of the polymyxin-based products included in the scope of this procedure remains positive, provided that changes, as applicable, are made to their product information as set out in Annex III to the opinion. Regarding the centrally-authorised product Colobreathe, the CHMP considered the product information to be up to date, with no need for revision.

Therefore, for the medicinal products referred to in Annex I, the CHMP recommended the variation to the terms of the marketing authorisation, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion. For Colobreathe, referred to in Annex A, the CHMP recommended the maintenance of the marketing authorisation, without any variations to the term of the marketing authorisation.

Grounds for the maintenance and the variation to the terms of the marketing authorisation, as applicable

Whereas

- the existing preclinical and clinical data and the product information including the indications, dosage recommendations and pharmacokinetic and pharmacodynamic information for polymyxin-based products in the EU are not up to date or based on robust data, as highlighted by recent reports of suboptimal efficacy and the emergence of colistin resistance,

- the CHMP carried out a benefit-risk evaluation of polymyxin-based products under Article 31 of Directive 2001/83/EC, reviewing all available data, including responses submitted by the marketing authorisation holders during the procedure and recommendations from the Pharmacokinetics and the Infectious Disease working parties,

- the CHMP considered that colistimethate sodium and colistin represent a crucial therapeutic option in the context of the treatment of infections caused by multi-drug resistant Gram-negative pathogens,

- the CHMP considered that the dose and strength of polymyxin-based products should continue to be expressed in international units,

- the CHMP considered the available data to be sufficient to support revisions of the indication for both parenteral use and inhalation use medicinal products, in line with clinical experience and current therapeutic guidelines
- the CHMP considered that the risks of nephrotoxicity and neurotoxicity observed with colistin for parenteral use should be balanced against the risk of the underlying disease and the high mortality from the treated conditions and that it can be satisfactorily mitigated by warnings and recommendations in the SmPC,

- the CHMP made extensive revisions to the SmPC to reflect current pharmacokinetic and pharmacodynamic data, including an update of the EUCAST breakpoints and the list of susceptible species,

The Committee, as a consequence, concluded that the benefit-risk balance of the polymyxin-based products included in the scope of this procedure remains positive under normal conditions of use, taking into account the agreed changes to the product information, as applicable.