Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

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

Zinnat contains cefuroxime axetil which is an oral pro-drug of cefuroxime, a second generation cephalosporin antibacterial agent. Cefuroxime exerts a bactericidal action by inhibiting bacterial enzymes necessary for cell-wall synthesis (peptidoglycan synthesis), thereby causing cell death. Zinnat was first approved in Europe in the late 1980's and is available as oral formulations. Zinnat was included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product. A referral under Article 30(2) of Directive 2001/83/EC was therefore triggered to resolve these divergences and thus harmonise the Product Information (PI) across the EU.

Section 4.1 - Therapeutic indications

The CHMP noted the large degree of divergences in the nationally approved indications and therefore reviewed the available data supporting each indvidual indication.

Acute streptococcal tonsillitis and pharyngitis

Having reviewed the submitted data, including studies by Aujard, 1995, Gooch, 1993 and Scholz, 2004, as well as studies by the German Society for Paediatric Infectious Diseases and an open, parallel group MAH-sponsored study conducted in general practice centres in the UK, France and Germany in 1989, the CHMP considered that the data supported the proposed indication.

Acute bacterial sinusitis

The CHMP noted that acute bacterial sinusitis is difficult to differentiate from the much more common viral sinusitis and that antibacterial treatment is often not warranted. However, having reviewed the submitted data, including studies by Kristo, 2005, Falagas, 2008, Zervos, 2003 as well as a Cochrane systematic review conducted by Ahovuo-Saloranta, 2008, a meta-anlysis by Young, 2008 and a systematic review by Ip, 2005, the CHMP considered the proposed indication to be acceptable.

Acute otitis media

Based on the submitted data, including studies by Hoberman, 2011, Tähtinen, 2011, Pessey, 1999, Gooch, 1996, McLinn, 1994, McLinn, 1990, Schwarz, 1991, Brodie, 1990 and Pichichero, 1990, the CHMP considered the proposed indication to be acceptable.

Community acquired pneumonia

The CHMP reviewed all available data and also noted that less susceptible pathogens cannot be managed by using higher doses of cefuroxime axetil than the maximum daily dose of 500 mg, due to the toxic degradation products of cefuroxime axetil and a lack of safety data. Having reviewed the minimum inhibitory concentrations (MIC) distributions for common respiratory pathogens such as penicillin-intermediate *S. pneumoniae, H. influenzae* and *M.catarrhalis* (Bulitta et al, 2009), the CHMP considered that the changes in MIC distributions over the last decades have impacted the suitability of cefuroxime axetil in this indication. The CHMP considered that no suitable dosing regimen could be identified to provide adequate coverage for less susceptible pathogens which have MIC up to 1 mg/L. The CHMP therefore concluded that cefuroxime axetil is not an appropriate agent for the empirical treatment of community acquired pneumonia and recommends the removal of this indication.

Acute exacerbations of chronic bronchitis

Having reviewed the submitted clinical documentation, which consisted of four adequately designed relatively large (>300 patients) double-blinded, comparative studies, the CHMP considered the proposed indication to be acceptable.

Urinary tract infections

The CHMP noted that no studies were provided to support the indication "urethritis" and therefore recommends the removal of this indication. Having reviewed the available data, the CHMP agreed that cefuroxime can be a valuable treatment option in the indications "*pyelonephritis*" and "*cystitis*", including in children and pregnant women and therefore considered these indications acceptable.

Gonorrhoea

The CHMP considered that treatment with cefuroxime axetil might not curtail further transmission of the infection. The CHMP also noted that the 2009 European Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults does not include cefuroxime on the list of antibiotics recommended in this indication, due to its suboptimal pharmacokinetic and pharmacodynamic (PK/PD) characteristics which may lead to worse effectiveness and to the selection of the resistant bacteria strains (Aison et al, 2004). Based on the available data, the CHMP concluded that cefuroxime axetil is not suitable in the treatment of uncomplicated gonorrhoea (urethritis and cervicitis) and therefore recommends the removal of the proposed indication.

Skin and soft tissue infections

The CHMP noted that the bacterial species most frequently involved in skin and soft tissue infections (i.e. staphylococci and streptococci) are sensitive to cefuroxime. Based on the available data, including one double blind study and several supporting studies, the CHMP concluded that there is sufficient data in support of the indication "*uncomplicated skin and soft tissue infections*".

Lyme disease

The CHMP reviewed the data from five randomised controlled studies, two of which included patients aged >12 years (Nadelman 1995; Lugar 1995), one which included patients aged >15 years (Cerar 2010), one study including children aged < 15 years (Arnez 1995) and one study including children aged between 6 months - 12 years. Based on the submitted study data, the CHMP considered the indication for the treatment of early Lyme disease to be acceptable.

In conclusion, the CHMP adopted the following harmonised indications and wording for Section 4.1:

"Zinnat is indicated for the treatment of the infections listed below in adults and children from the age of 3 months (see sections 4.4 and 5.1).

- *Acute streptococcal tonsillitis and pharyngitis.*
- *Acute bacterial sinusitis.*
- *Acute otitis media.*
- *Acute exacerbations of chronic bronchitis.*
- *Cystitis.*
- *Pyelonephritis.*
- *Uncomplicated skin and soft tissue infections.*
- *Treatment of early Lyme disease.*

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

Section 4.2 - Posology and method of administration

The CHMP noted the large degree of divergences in the nationally approved posologies and recommendations and therefore reviewed the available data to support a harmonised Section 4.2. The CHMP considered that the available clinical and PK/PD data confirm that a twice daily regimen of cefuroxime axetil is an effective dosage and that the use of cefuroxime axetil given three times daily is unsupported by the clinical and safety data. The CHMP reviewed the dosage recommendations for each individual indication and agreed that infections suspected or proven to be due to less susceptible bacterial species (such as penicillin intermediate *S. pneumonia*, *M. catarrhalis* and *H. influenzae*) should be treated with 500 mg administered every 12 hours. For the cystitis indication, the CHMP recommended an adult dosing regimen of 250 mg BID, to ensure adequate urinary concentrations of cefuroxime and thus the eradication of the key uropathogens implicated. In children, the CHMP similarly recommended a dosage of 15 mg/kg BID (250 mg twice daily up to 500 mg daily) for the cystitis indication. For Lyme disease, the CHMP considered that the existing clinical data supported treatment for 14 days, with a range of 10 to 21 days (European Union Concerted Action on Lyme Borreliosis, 2010), in adults and in paediatric patients. For the paediatric population, the CHMP agreed that the dosage should be 15 mg/kg twice daily, to a maximum of 250 mg twice daily. The section on paediatric patients was revised extensively, including a revision of the table of dosing recommendations for children below 40 kg to describe dosage and duration per indication as well as the dosing calculations depending on the patient's body mass. The CHMP also agreed on a cut-off age, stating that there is no experience of using Zinnat in children under the age of 3 months. In conclusion, the CHMP adopted harmonised posology recommendations for adults and children.

The CHMP inserted a statement advising that the cefuroxime axetil suspension formulation is not bioequivalent to the tablet formulation and are not substitutable on a milligram-per-milligram basis, due to differences in bioavailability and the time-concentration curve. The CHMP removed the option of parenteral-to-oral sequential therapy for all patients,, due to the significant reduction in exposure to the active drug when switching to the oral formulation.

Regarding patients with renal impairment, the CHMP reviewed the data and concluded that the proposed dosing guidelines in patients with renal impairment were acceptable. Regarding patients with hepatic impairment, the CHMP noted that there is no available data. In conclusion, the CHMP adopted a harmonised wording for Section 4.2.

Minor divergences in other sections of SmPC, labelling and package leaflet

The CHMP also adopted a harmonised wording for the remaining sections of the Zinnat SmPC and brought the labelling and the package leaflet in line with the adopted harmonised SmPC.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

The basis for this referral procedure was a harmonisation of the summary of product characteristics, labelling and package leaflet. Having considered the data submitted by the Marketing Authorisation Holder, the rapporteur and co-rapporteur assessment reports and the scientific discussions within the Committee, the CHMP was of the opinion that the benefit-risk ratio of Zinnat and associated names is favourable.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC,
- The committee considered the identified divergences for Zinnat and associated names regarding the therapeutic indications and the posology and method of administration sections, as well as in the remaining sections of the SmPC,
- The committee reviewed the data submitted by the MAH, including data from clinical trials, published literature and other clinical documentation, justifying the proposed harmonisation of the product information;
- The committee agreed the harmonisation of the summary of product characteristic, labelling and package leaflet proposed by the marketing authorisation holders,

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Zinnat and associated names (see Annex I).