9 November 2023
EMA/CHMP/456217/2023

CHMP List of questions

To be addressed by the marketing authorisation holder(s) for azithromycin-containing medicinal products for systemic use

Referral under Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1532

INN/active substance(s): azithromycin

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The marketing authorisation holders MAH(s) are requested to address the following questions:

Question 1

Information about the current wording of sections 4.1 to 5.3 of the SmPC of azithromycin-containing medicinal product(s) authorised in the EU/EEA should be provided in English in the tabular format in the Annex below, which also outlines the main differences between EU/EEA Member States.

Question 2

A justification of the current positive benefit-risk balance in all approved indications in the EU/EEA and for all age groups based on clinical efficacy and safety data from available clinical studies (with separate presentations on randomised and non-randomised studies) should be provided. The discussion should also consider information about resistance development against pathogens relevant for the approved indications in the EU/EEA as well as a risk assessment on the probability of development of resistance during treatment and recommendations in current national and European treatment guidelines.

Question 3

A discussion of the adequacy of the recommended dosage and duration of treatment for the approved indications should be provided, specifying the studies on which those recommendations are based and a detailed description of the underlying pharmacokinetic analyses including determination of the pharmacodynamic index (PDI), target attainment analyses and pharmacokinetic/pharmacodynamic (PK/PD) analyses for efficacy according to the *"Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/CHMP/594085/2015)"*. Furthermore, information about available PK data and population pharmacokinetic (PopPK) analysis from different age groups of paediatric population, elderly patients, patients with renal impairment and patients with hepatic impairment should be provided to justify the dosage and treatment duration in these populations.

Question 4

A scientific rationale for safety information (e.g. on the basis of clinical trial data or post-marketing data; on the basis of former scientific assessment by national competent authorities (NCAs) or EMA (e.g. PSUSA procedures)) in sections 4.3, 4.4 and 4.8 of the SmPC should be provided. The frequencies listed in section 4.8 should be justified based on safety data from clinical studies and post marketing period. In their response, the MAHs should report and discuss (status, ongoing/planned investigation, outcome) all safety reviews that have been performed by international regulatory authorities (if not already discussed at EU/EEA-level e.g. as part of variations, renewals and PSUSA or signal procedures). If there is any relevant late-breaking safety information (or aspects assessed in former EU/EEA assessments that have changed by now), please also discuss whether these should be reflected in the SmPC.

Question 5

A discussion of the adequacy of the data and information in sections 4.6 and 5.3 of the SmPC should be provided.

Question 6

Available data on clinically relevant interactions should be provided in the annexed table summarising this information to be included in section 4.5 of the SmPC. The following information should be given for each clinically relevant interaction if available: effect on C_{max}/AUC, mechanism (e.g. interaction due to inhibition/induction of cytochrome P450) and recommendation concerning co-administration with azithromycin.

Question 7

A discussion of the adequacy of data and information in sections 4.7, 4.9, 5.1 and 5.2 of the SmPC should be provided.

Question 8

Considering the responses to the above questions, a harmonised and up-to-date SmPC in English (sections 4.1 to 5.3 only, separately for oral and IV routes of administrations) and respective sections of the PL in line with the recommendations in the *"Guideline on summary of product characteristics"* and available QRD referral templates should be provided. The wording of the indications in section 4.1 of the SmPC should be in line with the recommendation in the *"Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 3)".* Further, the wording under section 4.6 of the SmPC and the respective section in the PL should be provided in accordance with the recommendations in the scientific *"Guideline on the risk-assessment-of medicinal-products-on human-reproduction and lactation: from data-labelling (EMEA/CHMP/203927/2005)"*.

Annex

Question 1

Section of the SmPC	**Current wording in azithromycin-containing medicinal product(s) authorised in the EU/EEA**	**Main differences in SmPCs between the EU/EEA Member States**
4.1 Therapeutic indication(s)		
4.2 Posology and method of administration		
4.3 Contraindications		
4.4 Warnings and precautions		
4.5 Interactions with other medicinal products		
4.6 Fertility, pregnancy and lactation		
4.7 Effects on ability to drive and use machines		
4.8 Undesirable effects		
4.9 Overdose		
5.1 Pharmacodynamic properties		
5.2 Pharmacokinetic properties		
5.3 Preclinical safety data		

Question 6

Active substances by Therapeutic Area	Interaction effect on C_{max}/AUC, (Possible mechanism)	Recommendation concerning co-administration