**NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC**
**E-mail:** [redacted]

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Germany:

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| Product Name (s) in the Referring Member State, if applicable | Azithromycin containing medicinal products |
| Active substance(s) | Azithromycin |
| Pharmaceutical form(s) | Pharmaceutical forms for systemic use |
| Strength(s) | All |
| Route(s) of administration(s) | Oral, intravenous |
| Marketing Authorisation Holder(s) | Various |

**Background**

The treatment of bacterial infections is hampered worldwide by the global spread of multidrug-resistant (MDR) or extensively drug-resistant (XDR) Gram-positive and Gram-negative pathogens and the lack of development of new antibiotics active against such MDR and XDR bacteria.

Azithromycin is a macrolide antibiotic inhibiting bacterial protein biosynthesis by binding to the 23S rRNA of the 50S ribosomal subunit. It is active against many aerobe Gram-positive and Gram-negative bacteria including intracellular pathogens such as *Chlamydia trachomatis*.

Resistance towards azithromycin is primarily conferred by overexpression of efflux pumps or modification of the target structure (e.g. methylation of the 23S ribosomal subunit by expression of *erm* (erythromycin ribososme methylase) genes, which leads to cross-resistance to macrolides, lincosamides and streptogramin B, the so-called $MLS_B$ phenotype).

Azithromycin-containing products for systemic use are authorised in the European Union (EU) as oral and intravenous formulations. Oral formulations are mainly indicated for the treatment of upper and lower respiratory tract infections, skin and soft tissue infections and uncomplicated genital infections in adults, adolescents and children while intravenous formulations are mainly indicated for treatment of community-acquired pneumonia and pelvic inflammatory disease in adults.

In addition to oral and intravenous formulations, a few topical azithromycin containing products are approved in EU Member States. However, the approved indications and posology of these products differ largely from that of systemic products. Furthermore, resistance data of topical azithromycin containing products are limited and difficult to assess. However, due to the limited use, a significant impact on the resistance development is not

expected. Therefore, a re-evaluation of the benefit-risk balance of topical products is not in the scope of this procedure.

**Issues to be considered**

Azithromycin is part of the World Health Organisation (WHO) Model List of Essential Medicines (2023) and WHO Model List of Essential Medicines for Children (2021) and has been classified into the WATCH category by WHO (AWaRe classification WHO 2017, confirmed in 2021[1]) which includes antibiotics with a higher potential for the selection of antimicrobial resistance and thus should be carefully monitored to avoid overuse. However, azithromycin is frequently prescribed in the EU for adult and paediatric patients (DARWIN study report C1-003[2]) and was increasingly used during COVID-19 pandemic in the hospital setting, as shown e.g. via German Antibiotic Consumption Surveillance (AVS)[3]. The data suggests that there is an overuse of systemic azithromycin in the EU, which can negatively influence the development of resistance.

Azithromycin resistance rates in the EU (based on systemic administration) are increasing for adults and paediatrics. For example, for *Neisseria gonorrhoea* a significant increase of minimum inhibitory concentrations (MICs) above the epidemiological cut-off (ECOFFs) threaten the effectiveness of the dual therapy of azithromycin plus ceftriaxone[4,5]. For other pathogens the trend is not that significant, however there was a relatively large increase in *S. pneumoniae* resistance to macrolides at EU/ EEA level in 2021 (+1.5%) compared to the reported rates in macrolide resistance at EU/ EEA level during the period 2017–2020[6]. Moreover, macrolide resistance rates for all age groups significantly differ between member states (MS) (e.g. resistance rate of 3.4-36.1% for *S. pneumoniae*).[6, 7]

In addition, since many azithromycin products were authorised decades ago by national procedures, there are significant differences between the product information of azithromycin-containing products across the EU MS, in particular in the approved indications and posology, but also in other sections of the product information. For oral azithromycin products the wording of several indications might be considered too broad (e.g. infections of the upper respiratory tract) which could promote overuse and resistance development. Furthermore, these indications are not in line with the recommendation in the current EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 3). Moreover, some rare indications, such as prophylaxis and treatment of disseminated infections by *Mycobacterium avium* complex in patients with advanced HIV infection or infections by *Helicobacter pylori*, are authorised in some EU MS only and there is a need to evaluate the benefit-risk balance based on available data.
In contrast, the authorised indications of intravenous azithromycin products are more harmonised across EU MS, however, concerns regarding increasing resistance rates are also applicable to those products.
Overall, the issues listed above (increasing resistance rate, high consumption rate and data suggesting overuse, different and broad indications in EU MS) may contrast in its current form the concept of a rational use of antibiotics and antibiotic stewardship considering the WHO categorisation of azithromycin.

Thus, there is a need to re-evaluate the benefit-risk balance of the azithromycin-containing products for systemic use in their approved indications considering the current scientific knowledge. Furthermore, the appropriate dose and duration of administration for both oral and intravenous formulations need to be discussed as well as the adequacy of safety relevant information and information about pharmacological properties.

In view of the above and given the necessity to take action at the EU level, Germany considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

References


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3. https://avs.rki.de/Content/ReferenceData/HospitalComparisonTime.aspx
4. Day, M.J., Jacobsson, S., Spiteri, G. *et al.* Significant increase in azithromycin "resistance" and susceptibility to ceftriaxone and cefixime in *Neisseria gonorrhoeae* isolates in 26 European countries, 2019. *BMC Infect Dis* **22**, 524 (2022).
5. https://www.ecdc.europa.eu/en/publications-data/gonococcal-antimicrobial-susceptibility-surveillance-2020
6. Antimicrobial resistance surveillance in Europe 2023; https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2023-2021-data
7. https://atlas.ecdc.europa.eu/public/index.aspx?Dataset=27&HealthTopic=4


Signed [redacted]

Date

30. Okt. 2023