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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Azithromycin-containing medicinal products for systemic use

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

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1. Information on the procedure

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 and 2023) 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 C1-0032[1]) and was increasingly used during COVID-19 pandemic in the hospital setting, as shown e.g. via German Antibiotic Consumption Surveillance (AVS). 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 gonorrhoeae* 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. For other pathogens the trend is not that significant, however there was a relatively large increase in *Streptococcus 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. Moreover, macrolide resistance rates for all age groups significantly differ between member states (MS) (e.g. resistance rate of 3.4-36.1% for *Streptococcus pneumoniae*).

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/EEA, 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/EEA Member States (MSs) 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/EEA MSs, 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/EEA 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.

[1] https://catalogues.ema.europa.eu/node/3659/administrative-details

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. Resistance data of topical azithromycin containing products are limited and difficult to assess due to lack of European committee on antimicrobial susceptibility testing (EUCAST) breakpoints. 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.

On 30 October 2023 the National Competent Authority in Germany therefore triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of azithromycin-containing medicinal products for systemic use and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure is thus limited to systemic (oral and parenteral) formulations of azithromycin.

2. Scientific discussion

2.1. Introduction

Azithromycin is a macrolide antibiotic inhibiting bacterial protein biosynthesis by binding to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

It is active against many aerobic 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 ribosome methylase) genes, which leads to cross-resistance to macrolides, lincosamides and streptogramin B, the so-called MLSB phenotype).

Azithromycin-containing products for systemic use are authorised in the European Union (EU) mainly as oral and intravenous formulations. Azithromycin for oral administration is authorised for the treatment of children, adolescents and adults and is available as 125 mg, 250 mg, 500 mg, 600 mg tablets/capsules, as 250 mg, 500 mg, 600 mg, 1000 mg dispersible tablets, as powder for oral suspension in bottle (20 mg/ml and 40 mg/ml), in sachet (100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 1000 mg) and as granules of oral suspension, for all pharmaceutical forms expressed as azithromycin (the active substance is usually azithromycin dihydrate).

Azithromycin for oral administration is authorised in most Member States (MS) for the following indications, with variations in the wordings of the indications:

- Infections of the upper respiratory tract including sinusitis, pharyngitis, tonsillitis
- Infections of the lower respiratory tract including acute exacerbation of chronic bronchitis and pneumonia
- Acute bacterial otitis media
- Skin and soft tissue infections (folliculitis, cellulitis, erysipelas, impetigo and secondary purulent dermatitis)

- Uncomplicated infections of the genital tract in women by *Chlamydia trachomatis* or non-multiresistant *Neisseria gonorrhoeae* (cervicitis)
- Uncomplicated genital infections in men due to *Chlamydia trachomatis* or non-multiresistant *Neisseria gonorrhoeae* (urethritis)

While azithromycin for oral administration is only authorised in single MS for the following indications, with variations in the wordings of the indications:

- Erythema migrans (the first symptom of Lyme disease)
- Moderate acne vulgaris
- Treatment of chancroid/soft ulcer caused by *Haemophilus ducreyi* in men
- Chronic prostatitis caused by *Chlamydia trachomatis*
- Prophylaxis of disseminated infections caused by organisms of the *Mycobacterium avium* complex (MAC) alone or in combination with rifabutin in patients with advanced HIV infection
- Treatment of disseminated infections caused by organisms of the MAC in patients with advanced-stage HIV infection
- Periodontal abscesses and periodontitis
- Exacerbations of eosinophilic and non-eosinophilic asthma
- Gastro-duodenal infections caused by *Helicobacter pylori*

Azithromycin for intravenous administration is authorised in most Member States and only for treatment of adult patients. Azithromycin is available as 500 mg powder for solution for infusion for the following indications, with minor variations in the wordings of the indications:

- community-acquired pneumonia and
- pelvic inflammatory disease / uncomplicated ascending adnexitis.

In addition, the CHMP noted that azithromycin is in the WHO Model List of Essential Medicines first choice for cholera and enteric fever, and the second choice for acute invasive bacterial diarrhoea, however it is currently not authorised in the EU for these indications.

In addition to data from DARWIN and AVS mentioned above, based on the data reported in PSUSAs and calculated as 5 day treatment courses, it is estimated that approximately 300 million patients were exposed to azithromycin containing products between 2017 and 2020, while approximately 465 million patients were exposed between 2020 and 2023, which corresponds to a 1.55-fold increase in exposed patients.

Azithromycin resistance rates in the EU (based on systemic administration) are increasing for adults and paediatric patients, while due to the divergent national decisions taken by MS concerning the authorisation of azithromycin-containing products for systemic use decades ago, there are significant differences between the product information of azithromycin-containing products across the EU MS in the approved, partly broad, indications (some authorised in a few individual Member States only), and posology, but also in other sections of the product information.

In contrast, the authorised indications of intravenous azithromycin products are more harmonised across EU/EEA MSs, however, concerns regarding increasing resistance rates are also applicable to those products.

Overall, there was a need to re-evaluate the benefit-risk balance based on available data in all of the indications of azithromycin containing products for systemic use.

The CHMP considered all available data, including non-clinical and clinical studies, epidemiological studies, susceptibility testing data and scientific literature. A summary of the most relevant data is included below.

2.2. Data on efficacy

Data on clinical efficacy and safety data from available clinical studies, considering information about resistance development against pathogens relevant for the approved indications in the EU/EEA were evaluated in order to review the benefit-risk balance for all age groups. Recommendations in current national and European treatment guidelines were also considered. Relevant data are summarised below.

2.2.1. Lower respiratory tract infections (LRTI) including bronchitis and pneumonia

The indications related to infections of the lower respiratory tract, covering bronchitis and pneumonia to various degrees, are approved in the EU in azithromycin-containing oral products for children and adults. The indication Community-acquired pneumonia (CAP) is approved in azithromycin-containing products for IV use in adults only.

Lower respiratory tract infections include the following entities: acute bronchitis (AB), community acquired pneumonia, acute exacerbations of chronic obstructive pulmonary disease/chronic bronchitis (AECB), and acute exacerbation of bronchiectasis (AEB). The typical common causative pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenza*. Rare pathogens are Enterobacterales (*Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*) and *Pseudomonas aeruginosa*. Atypical pathogens include *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Chlamydia psittaci*. Empirical treatment plays the dominant role in the management of lower respiratory tract infections.

The spectrum of *in-vitro* activity of azithromycin includes the following pathogens relevant for these indications: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis, Legionella pneumophila*, and *Chlamydophila pneumonia*.

Community-acquired pneumonia (CAP)

CAP is an acute infection of the pulmonary parenchyma acquired outside of the hospital with *Streptococcus pneumoniae* being the primary bacterial pathogen. The clinical presentation of CAP varies, ranging from mild pneumonia characterised by fever and productive cough to severe pneumonia characterised by respiratory distress and sepsis. Because of the wide spectrum of associated clinical features, CAP is a part of the differential diagnosis of nearly all respiratory illnesses.

Clinical studies sponsored by MAH(s)

The initial Pfizer clinical trial documentation for the treatment of lower respiratory tract infections with the oral formulations comprised 12 studies in which 755 patients aged 16 and older received azithromycin. In the initial filing, 7 studies (117, 326, 103, 106, 109, 303 and 313 [5 open label comparative studies and 2 double-blind studies]) were used to support the claim of effectiveness of azithromycin in lower respiratory tract infections (Table 1). Randomised, comparative studies 103 and 106 were terminated after enrolling only few patients and are not further relevant for the purpose of this procedure.

Table 1: Numbers of pneumonia patients ≥16 years of age treated with azithromycin or comparator in Pfizer studies to support the pneumonia indication

103(US)	1	Erythromycin (1)
106 (Non US)	6	Erythromycin (6)
109 (US)	9	Cefaclor (8)
117 (US)	14	Cefaclor (23)
303 (Non US)	21	Erythromycin (21)
313 (Non US)	4	Augmentin (4)
326 (Non US)	8	Amoxicillin (8)
Total	**63**	**71**

The results from one comparative open-label study in LRTIs (protocol 109) and one double-blind study (protocol 117) in pneumonia patients showed that azithromycin (500 mg on the first day of therapy followed by 250 mg/day for 4 days) was bacteriologically and clinically as effective as a standard regimen of cefaclor in the treatment of pneumonia in the few patients included in the studies.

Out of all seven studies submitted, only 22 patients were treated with azithromycin and evaluable for efficacy in pneumonia. For azithromycin IV, five Phase 3 clinical trials were conducted in the treatment of CAP and study 94CE33-0649 was conducted in Legionella patients. One further study was terminated early due to poor enrolment (study 066-138). Of the five CAP studies, two were conducted in the US and are considered pivotal to this indication (studies 066-0618 and 066-0625); the remaining three non-US CAP studies are supportive studies (Studies 066-349, 066-350 and 066-359).

Other published studies

Results of numerous clinical trials in which five or three-day azithromycin therapy was compared with amoxicillin, co-amoxiclav, clarithromycin, erythromycin, nemonoxacin, cethromycin azithromycin and levofloxacin which were applied for seven to fourteen days, have been presented. The reviews of Pakhale et al. in 2014, Laopaiboon et al. (2015) and Al-Salloum et al. (2021) analysing multiple trials concluded that azithromycin is an effective, safe and well-tolerated drug in the treatment of community-acquired pneumonia in adults.

The results from RCTs published by Ferwerda et al. (2001) and Kogan et al. (2003), support the results from initial clinical studies for the treatment of CAP in children. In another systematic review of six publications (cohort studies and randomised controlled trials) by Al Saeedy et al., (2021) comparing efficacy of beta lactams and macrolides in the treatment of paediatric pneumonia, use of macrolides as monotherapy or add-on therapy to beta-lactams was found to be more effective where within the macrolide class, azithromycin was more clinically significant compared to erythromycin.

Guideline recommendations

For treatment of CAP in adults, the European Guidelines for the management of adult lower respiratory tract infections (Woodhead et al., 2005) states that macrolides may be used for the treatment of CAP in combination with penicillin G, aminopenicillin, co-amoxiclav or 3rd cephalosporin in a hospital setting only. This is in line with the ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia (sCAP) that recommend the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in hospitalised patients with sCAP. According to the NICE 2019 guidelines for the treatment of community-acquired pneumonia (CAP), for adults with non-severe CAP who cannot take amoxicillin, doxycycline, or clarithromycin due to contraindications or intolerance, azithromycin is suggested as an alternative.

For treatment of CAP in children, an update in management of CAP in children was published by Carpenter & Hofto (2023). Outside of the neonatal period, parenteral penicillin or ampicillin is recommended as first-line therapy for otherwise healthy children hospitalised with uncomplicated

pneumonia. In cases of serious penicillin allergies, levofloxacin, linezolid, azithromycin, or clindamycin are options. This is also in line with other national guidelines (Germany, Poland, and Czech Republic).

Atypical pneumonia

Atypical pathogens are intracellular bacteria causing CAP in a significant minority of patients. *Legionella* spp., *Chlamydia pneumoniae* and *psittaci*, and *Mycoplasma pneumonia* are commonly included in this category. *Mycoplasma pneumoniae* is present in 5–8% of CAP, being the second most frequent pathogen after *Streptococcus pneumoniae*. *Legionella pneumophila* is found in 3–5% of inpatients and *Chlamydia* spp. is present in less than 1% of patients (Garin et al 2022).

Clinical studies

Sánchez et al. (1998) studied 19 patients with pneumonia caused by *Legionella*, Sáez-Llorens et al. (1998), conducted a study to determine the importance of *Mycoplasma pneumonia* and *Chlamydia pneumoniae* in community-acquired pneumonia (CAP), and Kogan et al. (2003) compared the clinical efficacy of azithromycin vs. erythromycin and amoxicillin in the treatment of presumed bacterial community-acquired pneumonia in ambulatory children and all authors found azithromycin to be as efficacious in the treatment of atypical pneumonia, as the other antibiotics. The authors concluded that azithromycin is an effective therapeutic option for the treatment of community-acquired classic and atypical pneumonia in children. In addition, study 94CE33-0649 (pneumonia due to *Legionella pneumophila*) is also considered relevant to support the CAP indication for the IV formulation of azithromycin.

Guideline recommendations

The annotated British Thoracic Society (BTS) Guideline for the management of CAP in adults (2015) recommends an oral fluoroquinolone for low and moderate severity community acquired *Legionella* pneumonia. In the unusual case when this is not possible due to patient intolerance, a macrolide is an alternative. Antibiotics are not required for the non-pneumonic self-limiting form of legionellosis (pontiac fever). For the management of high severity or life-threatening legionella pneumonia, a fluoroquinolone is recommended. For the first few days this can be combined with a macrolide (azithromycin is an option in countries where it is used for pneumonia) or rifampicin as an alternative. Clinicians should be alert to the potential small risk of cardiac electrophysiological abnormalities with quinolone-macrolide combinations.

According to the German guideline "Management of Adult Community-acquired Pneumonia and Prevention – Update 2021", azithromycin may be given as alternative therapy in case of atypical pneumonia caused by *Legionella* spp., *Mycoplasma pneumonia* or *Chlamydophila pneumonia*.

Acute bronchitis (AB)

AB is a common clinical condition characterised by an acute onset but persistent cough, with or without sputum production. It is typically self-limited, resolving within one to three weeks. Symptoms result from inflammation of the lower respiratory tract and are most frequently due to viral infection.

Clinical studies

The Pfizer clinical trial documentation for the treatment of acute bronchitis initially comprised 5 studies in which seven-hundred-seventy patients were enrolled and treated with azithromycin (study 421), or comparators. The table shows the numbers of patients, all ≥16 years of age, who were enrolled in each of the studies supporting the bronchitis claim.

Table 2: Pfizer studies supporting the bronchitis claim

Protocol	Azithromycin N	Comparator N
Bronchitis		
103(US)	22	Erythromycin (26)
109 (US)	146	Cefaclor (69)
303 (Non US)	72	Erythromycin (66)
313 (Non US)	48	Augmentin (54)
326 (Non US)	133	Amoxicillin (134)
Total	**421**	**349**

These five studies also included patients with CAP as described above, and only 133 patients were treated with azithromycin and considered evaluable for efficacy in acute bronchitis.

These 5 comparative studies found azithromycin (500 mg on the first day of therapy followed by 250 mg/day for 4 days, or 500 mg/day for 3 days) to be bacteriologically more effective than a standard regimen of amoxicillin and is as effective as standard regimens of erythromycin, cefaclor, or amoxicillin/clavulanic acid in the treatment of bronchitis caused by *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp. Also, azithromycin is clinically more effective than cefaclor and is as effective as erythromycin, amoxicillin, or amoxicillin/clavulanic acid in treating patients with bronchitis.

Reviews in which azithromycin therapy was compared to other antibiotics in acute bronchitis have been presented, for example the review by Killeen and Wolfson (2020) assessed the effect of antibiotics in patients with acute bronchitis in a Cochrane review and concluded that antibiotics including azithromycin provide only small benefits in cough and activity level in patients with acute bronchitis.

Limited evidence of clinical benefit to support the use of antibiotics in acute bronchitis was also reported in a meta-analysis including 17 randomised controlled trials covering 5099 participants (Smith SM. et al., 2014, update 2017). The authors also concluded that antibiotics may have a modest beneficial effect in some patients such as frail, elderly people with multimorbidity who may not have been included in trials to date.

Guideline recommendations

The NICE guideline for acute cough (2019) and Albert et al. (2010) suggest that antibiotics should not routinely be offered to people (adults or children) with an acute cough associated with acute bronchitis. This is in line with other EU/EEA national recommendations (e.g. France).

Acute exacerbation of chronic bronchitis (AECB)

AECB is a sustained worsening of a chronic bronchitis patient's symptoms from their usual stable state, which is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour.

Clinical studies

The initial Pfizer clinical trial documentation for the treatment of AECB comprised two studies (109 mentioned above, and 315), which found that cure and bacterial eradication occurred in the majority of patients.

Results of numerous clinical trials in which azithromycin therapy was compared to other antibiotics have been presented. Schouenborg et al. (2000) found similar success rates of a 3-days azithromycin 500 mg OD regimen compared to 10 days pivampicillin (700 mg BID), and Siempos et al. 2007 found

no statistically robust differences in a meta-analysis covering 7405 patients regarding treatment success in intention-to-treat and clinically evaluable patients between (a) macrolides and quinolones, (b) azithromycin/clavulanic acid (A/C) and quinolones, or (c) A/C and macrolides.

The authors concluded that macrolides, quinolones and pivampicillin may be considered equivalent for the treatment of patients with an acute bacterial exacerbation of chronic bronchitis in terms of short-term effectiveness.

Guideline recommendations

According to The European Guidelines for the management of adult lower respiratory tract infections (Woodhead et al., 2005, updated 2011), tetracycline and amoxicillin are first-choice antibiotics for treatment of mild COPD without comorbidities. Macrolides are not recommended as first line treatment for acute exacerbations of COPD (AECB) because of reduced activity against *Haemophilus influenzae*, and very high rates of pneumococcal resistance to macrolides in many European countries but could be used when local bacterial resistance rates impair effectiveness of first choice agents and in in case of intolerance to these agents. Moreover, for treatment of moderate to severe COPD, macrolide antibiotics are generally not recommended. This recommendation is in line with the NICE guidelines on acute exacerbation of chronic pulmonary disease (2018) and other national guidelines (France).

Acute exacerbation of bronchiectasis (AEB)

Bronchiectasis is a heterogeneous chronic respiratory disease that is characterised by frequent respiratory infections. In general, it is common belief that most of the exacerbations of bronchiectasis in adults are infectious events.

Clinical studies

Altenburg et al (2013) and Goyal et al (2018) conducted randomised double-blind studies where azithromycin has demonstrated its efficacy in the treatment of infectious exacerbations among patients with bronchiectasis. They found that among adults with non-CF bronchiectasis, the daily use of azithromycin for 12 months resulted in a lower rate of infectious exacerbations compared with placebo, and that azithromycin is non-inferior to amoxicillin clavulanate for resolving exacerbations in children with non-severe bronchiectasis in children 1-9 years of age, respectively. However, Altenburg et al. 2013 found a macrolide resistance rate of 88% in azithromycin-treated individuals, compared with 26% in the placebo group.

Guideline recommendations

The European Guidelines for the management of adult lower respiratory tract infections (Woodhead et al., 2005, updated 2011) does not mention macrolide antibiotics for the treatment of AEB. However, the European Respiratory Society guidelines for the management of adult bronchiectasis (Polverino et al. 2017) suggests long-term treatment with macrolides (azithromycin, erythromycin) for adults with bronchiectasis and chronic *P. aeruginosa* infection in whom an inhaled antibiotic is contraindicated, not tolerated or not feasible. Moreover, long-term treatment with macrolides (azithromycin, erythromycin) is indicated in addition to or in place of an inhaled antibiotic, for adults with bronchiectasis and chronic *P. aeruginosa* infection who have a high exacerbation frequency despite taking an inhaled antibiotic. Further, long-term treatment with macrolides is suggested for adults with bronchiectasis not infected with *P. aeruginosa*. However, these long-term treatment regimens are not currently authorised posologies for azithromycin containing products and have been shown to lead to macrolide resistance rate of 88% following 12 months of azithromycin (Altenburg et al. 2013, Polverino et al. 2017).

Resistance development in LRTIs

Resistance depends on the strain, e.g. for *Streptococcus pneumoniae*, convincing European surveillance data were presented, which indicated a sustaining problem of acquired resistance in this species in the range of 20% (but a longitudinal decline over time in susceptibility to azithromycin has not occurred (WHO Europe 2022, ECDC, 2020 and 2022, ATLAS 2017 and SENTRY 2022). National data varied in the level of acquired resistance ranging from 8-10 % in Germany to 26.5 % in Poland. On a national level, e.g. in HR, pneumococcal macrolide resistance is also decreasing but remains on a high level (32% in 2018 to 24% in 2022) (Andrašević et al., 2022). According to Zhanel et al. (2014), per 100 subjects treated empirically with azithromycin, an additional 3.1 clinical failures would be predicted, as a consequence of azithromycin resistance (low and high level resistance).

Additionally, penicillin-susceptible strains of *Streptococcus pneumoniae* (PSSP) are more likely to be susceptible to azithromycin than penicillin-resistant strains of *Streptococcus pneumoniae* (PRSP). The EU/EEA population-weighted mean percentage for combined penicillin non-wild-type and resistance to macrolides was 9.7% in 2022, with a significantly increasing trend during the period 2018−2022 (ECDC, 2022). There is a notable correlation between the penicillin G Minimum Inhibitory Concentration (MIC) and macrolide resistance. Strains with higher penicillin G MICs are more likely to exhibit resistance to macrolides, including azithromycin. Numerous studies highlighted a high prevalence of co-resistance between penicillin and azithromycin, underscoring the complexity of treating infections caused by *Streptococcus pneumoniae*. With regard to the data from the EARS-Net report 2022, for both, PSSP and PRSP, acquired resistance may be a problem (resistance level above 10% threshold).

For *S. aureus*, the evidence suggests susceptibility rates over time against *S. aureus* (around 70% and higher) have remained stable since 2018, (SENTRY and ATLAS databases).

National data from Poland showed high and common susceptibility of *Haemophilus influenzae* for azithromycin and clarithromycin between 2005 and 2019 and in 2022. The SENTRY and ATLAS Surveillance Programmes found that azithromycin susceptibility in *Haemophilus influenzae* isolates collected from medical centres in Europe during 2019-2022 and 2018-2022 respectively, was high and in the range of 99%. Cadenas-Jiménez et al. (2024) and Carrera-Salinas et al. (2022) found that high susceptibility of persistent lineages of *Haemophilus influenzae,* some of them isolated before treatment.

National data from Portugal indicate that acquired resistance may be a problem for *Legionella pneumophila* (azithromycin-resistance in 12 of 100 clinical isolates collected between 2006 and 2022), but the number of isolates was very limited. Because of the fastidious nature of the organism, no gold standard for antimicrobial susceptibility testing of *Legionella pneumophila* exists. According to the EUCAST guidance on *Legionella*, acquired antimicrobial resistance in *Legionella pneumophila* is rare. While there may be laboratory evidence of reduced susceptibility of *Legionella pneumophila* to azithromycin, interpretation of the results and comparison with other resistance data might be limited.

Common susceptibility (1-10% resistance) was reported for *Mycoplasma pneumoniae* in SE in 2022. Multiple review articles indicate low level macrolide resistance in *Mycoplasma pneumoniae* in the European region. However, local resistance might exceed the 10% threshold, e.g. in Italy, but recent data is often missing. National data from Slovenia, Germany and Spain underpin the outcome of the review articles.

Swedish data from 2022 indicate a common susceptibility of *Chlamydia trachomatis* and *Chlamydophila pneumoniae* with low level AZM-resistance (<1%), indicating low level "category 1" resistance.

2.2.2. Upper respiratory tract infections (URTIs) including sinusitis, pharyngitis, and tonsillitis

Sinusitis

Acute rhinosinusitis (ARS) is defined as symptomatic inflammation of the nasal cavity and paranasal sinuses lasting less than four weeks. The most common aetiology of ARS is viral infection. Only about 2% of cases are complicated by bacterial infection. The most common bacterial pathogens identified in ARS are *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Acute bacterial rhinosinusitis (ABRS) is commonly a self-limited disease.

Clinical studies

The Pfizer clinical trial documentation for the treatment of sinusitis initially comprised 3 studies conducted in 1987/1988 in which 228 patients aged 16 or older received azithromycin.

Study 113 and 314 (1988) were multicentre, open-label, randomised trials comparing azithromycin (500 mg on day 1 followed by 250 mg/day for 4 days) and amoxicillin (500 mg TID for 10 days) found that clinical response and bacterial eradication was comparable in in both treatment groups.

Study 302 (1987), an open, multicentre study to assess the safety and efficacy of azithromycin compared to erythromycin in the treatment of upper respiratory tract infections. Clinical cure was reported for 83% of azithromycin patients and 79% of erythromycin patients. Bacterial eradication was reported for 87% of azithromycin patients and 86% of erythromycin patients.

Published results from RCTs support the results from studies 113, 314, and 302, e.g. Casiano et al. (1991) and Alagić-Smailbegović et al (2006).

Guideline recommendations

According to the current NICE guideline for the treatment of the acute sinusitis, first-choice oral antibiotic is phenoxymethylpenicillin in adults and in children. Alternative first choices for penicillin allergy or intolerance (for people who are not pregnant) are doxycycline and clarithromycin.

National Guidelines from Czechia and Germany reflect current NICE guidance from UK (NICE) and US (American Academy of Otolaryngology—Head and Neck Surgery Foundation) that first-choice oral antibiotic is phenoxymethylpenicillin or amoxicillin with or without clavulanate in adults and in children Macrolide antibiotics and trimethoprim-sulfamethoxazole are not recommended for initial therapy of ABRS (Rosenfeld et al 2015).

Resistance development

Resistance data for *Streptococcus pneumoniae* and *Haemophilus influenzae* have been described in the section on LRTI above. According to data from the SENTRY database, *Moraxella catarrhalis* is commonly susceptible to azithromycin, indicating low level "category 1" resistance.

Pharyngitis

Acute pharyngitis (AP) is a common infectious disease in adults and children with mostly viral aetiology. The main bacterial pathogens are group A *β-haemolytic streptococci* (GABHS), i.e. *Streptococcus pyogenes.*

Clinical studies

The Pfizer clinical trial documentation for the treatment of pharyngitis initially comprised 5 studies in which 406 patients (including paediatric subjects) received azithromycin. Three studies conducted in 1988/1989 were designed to recruit adult patients with pharyngitis: one double blind, comparative

study was conducted in the U.S. (116) versus penicillin V, two U.S. studies were of open label, randomised, comparative design, versus erythromycin (102) and penicillin V (108), which found all comparable efficacy in terms of clinical improvements or bacterial eradication.

For the treatment of pharyngitis in the paediatric population, a total of 842 children were enrolled in 3 multicentre double-blind comparative trials that comprise the primary efficacy database (163, 163Z, 175) and randomised to therapy with azithromycin (422 patients) or penicillin V (420 patients). Moreover, results of 2 additional U.S. studies (126 and 126Z) and 5 non-U.S. studies (306, 321, 335, 397, and 398) of azithromycin in the treatment of pharyngitis were presented, which found either better (163, 175, 163Z) or similar efficacy and safety compared with penicillin V (321, 306, 126, 126Z, 355) in 3-day and 5-day regimens.

Literature data

Results of numerous clinical trials in which five or three-day azithromycin therapy was compared with penicillin V, erythromycin, clarithromycin, roxithromycin or cefaclor which were applied for a ten-day period, have been presented by Hedin et al. (2023), Hooton (1991), O'Doherty et al. (1996) and Koga et al. (2011).

All authors concluded that azithromycin appears to be a safe and effective alternative treatment for streptococcal pharyngitis/tonsillitis in children and adults.

Guideline recommendations

Pellegrino et al. 2023 performed a comparison of 19 current recommendations from national and international guidelines for the treatment of acute pharyngitis in children and adults. Three groups of the guidelines can be distinguished: one group supports the antibiotic treatment of group A β-haemolytic Streptococcus (GABHS) to prevent acute rheumatic fever (ARF), the second considers acute pharyngitis a self-resolving disease, recommending antibiotics only in selected cases and the third group recognises a different strategy according to the ARF risk in each patient. An antibiotic course of 10 days is recommended if the prevention of ARF is the primary goal; conversely, some guidelines suggest a course of 5–7 days, assuming the symptomatic cure is the goal of treatment. Penicillin V and amoxicillin are the first-line options. In the case of penicillin allergy, first-generation cephalosporins are a suitable choice. In the case of beta-lactam allergy, clindamycin or macrolides (including azithromycin) could be considered according to local resistance rates.

According to treatment guidelines from CDC, IDSA, NICE, and France, azithromycin is not the substance of first choice for the treatment of acute pharyngitis and tonsillitis, however, it may be an alternative in case of beta-lactam allergy.

Tonsillitis

Acute tonsillitis (AT) is mainly caused by viruses. The most important pathogens that cause bacterial tonsillitis are GABHS, i.e. *Streptococcus pyogenes*. Generally, a clear differentiation between GABHS-induced pharyngitis and tonsillitis is not possible and results from RCTs and guideline recommendations apply to both entities.

Clinical studies

Li et al. (2019) conducted an RCT to evaluate the clinical efficacy of azithromycin, cefaclor, and amoxicillin in treatment of paediatric tonsillitis (256 children enrolled) in a 3-,5- and 10-day treatment regimen respectively, and found comparable outcomes in terms of clinical success and bacterial eradication.

Hamill et al., (1993) found that once-daily azithromycin for three days is clinically equivalent to ten days of penicillin V qid in the treatment of children with acute pharyngitis or tonsillitis caused by GABHS.

Guideline recommendation

The ESCMID, NICE and Czech guidelines state that if antibiotics are indicated for the treatment of streptococcal tonsillopharyngitis in children, phenoxymethylpenicillin is the first-choice treatment; amoxicillin could be an alternative. In case of penicillin allergy or intolerance, clarithromycin or spiramycin may be used.

Similar to the indications sinusitis and pharyngitis, macrolides are only alternatives in case of allergy or intolerance to penicillin.

Resistance development (pharyngitis and tonsillitis)

For *S. pyogenes*, a recent trend for increasing resistance was observed in the ATLAS and SENTRY databases (16.25% in 2021, 160 isolates; and 15.9% in 2022, 107 isolates), whilst the previous resistance rates were below 10% threshold, respectively. Since the sample-size of the databases was quite limited, the recent increase in azithromycin-resistance in *S. pyogen*es might be an artefact. National data from PL (8.9% in 2022, similar to the resistance levels in 2019 and 2020; an exception was the year 2021, where 25.6% of isolates showed resistance to erythromycin.), SE (1–10% in 2022), and FR (10% in 2021, 5% resistance in group A streptococci in 2022) do not exceed the 10% threshold, indicating common susceptibility.

2.2.3. Acute otitis media

The indication acute otitis media (AOM) is approved for orally administered azithromycin-containing medicinal products for paediatric population and adults.

AOM in the paediatric population

Acute otitis media is one of the most common inflammatory disorders in children and includes ear pain, ear rubbing, hearing loss and ear drainage. Fever occurs in about 2/3 of the patients. It is an acute, suppurative infectious process characterised by the presence of infected middle ear fluid and inflammation of the mucosa lining the middle ear space. The infection is most commonly triggered by a dysfunction of the Eustachian tube, which leads to a backflow and suppuration of retained secretions. AOM can also be associated with purulent otorrhoea if the tympanic membrane is ruptured. Due to the easier ascent of pathogens through the shorter Eustachian tube, children are particularly affected.

The most common bacterial pathogens are *Streptococcus pneumoniae* (caused more than 50% of paediatric AOM cases worldwide) and *Haemophilus influenzae* (responsible for approximately 20% of AOM episodes in children aged <6 years), followed by *Moraxella catarrhalis* (prevalence rate of approximately 10-1%). *Streptococcus pyogenes*, *Staphylococcus aureus*, Viridians streptococci, and *Pseudomonas aeruginosa* are found in smaller numbers. Group A Streptococcus and *Staphylococcus aureus* are less common causes of AOM in the general paediatric population. In addition, Group A Streptococcus may be an important pathogen in patients with severe AOM requiring hospitalisation.

A viral upper respiratory infection is a common predisposing factor for AOM in children, and viruses may coinfect the middle ear along with bacteria.

The spectrum of activity of azithromycin includes the following pathogens relevant for the indication AOM: *Moraxella catarrhalis, Streptococcus pyogenes* are commonly susceptible species. *Streptococcus pneumoniae, Staphylococcus aureus* are species for which acquired resistance may present a problem

during use. According to EUCAST, the clinical evidence for the efficacy of azithromycin in *Haemophilus influenzae* respiratory infections is conflicting due to high spontaneous cure rates.

Clinical trials with 5-day dosing regimen:

For the treatment of otitis media, a total of 1,574 children were enrolled in 4 multicentre clinical trials conducted by Pfizer Central Research in the US. These studies comprise the primary efficacy database (studies 128, 134, 178 and 176) and randomised to intended therapy with the 5-day dosing regimen of azithromycin (890 patients) or Augmentin (684 patients). One study (134) was a double-blind comparative trial versus Augmentin, 2 (studies 128 and 178) were open-label comparative trials versus Augmentin, and 1 (study 176) was an open-label non-comparative trial. These studies showed that a 5-day OD azithromycin regimen (10 mg/kg once on day 1 followed by 5 mg/kg once daily) in paediatric AOM was comparably efficacious to amoxicillin 40mg/kg/day + clavulanate TID in a 10-days regimen.

In addition to the 4 US studies listed above, the results of two non-US studies of azithromycin in the treatment of AOM have been presented by Pfizer (studies 322 and 334 studied azithromycin 5-days vs Augmentin 10-days dosing regimen in children 5-15 years and 2-5 years, respectively), which both found higher cure rates for azithromycin than Augmentin in AOM.

Clinical trials with accelerated 1- and 3-day dosing regimen

Following initial regulatory approvals for the 5-day dosing regimen, additional paediatric studies were conducted to support the use of azithromycin using the dosing regimen of 30 mg/kg given as a single dose or given over 3 days (10 mg/kg/day) for otitis media. In the 4 pivotal otitis media trials (R-0581, A0661015, AZM-NY-95-001, A0661014), a total of 1,169 children aged 6 months to 12 years were randomised and 741 received treatment with azithromycin at a dose of 30 mg/kg, either as a single dose (n = 487), or as a regimen of 10 mg/kg/day for 3 days (n = 254), and 424 subjects received comparators (amoxicillin, amoxicillin/clavulanate or ceftriaxone). These studies found that that:

- a single dose of azithromycin is as safe and effective as amoxicillin/clavulanate in the treatment of otitis media in paediatric patients (R-0581).
- a single dose of 30 mg/kg was effective in promoting resolution of the signs and symptoms of acute otitis media (Study A0661015).
- satisfactory and comparable clinical responses were found for azithromycin 1-day patients, azithromycin 3-day patients and ceftriaxone patients (Study AZM-NY-95-001).
- similar clinical success (cure) was reported for azithromycin patients (3-day regimen) compared to 10 days of amoxicillin/clavulanate (Study A0661014).

In addition, 2 non-US trials 337, and 394 studied this dosing regimen found that azithromycin 3 days was either superior (study 337) or comparable (study 394) to 10 days amoxicillin in terms of clinical responses.

A recent systematic review and meta-analysis of the efficacy and safety of azithromycin and amoxicillin/clavulanate in the treatment of otitis media in children from Dawit et al. (2021) support the results from the above-mentioned clinical studies. The meta-analysis results showed no statistically significant difference in efficacy in favour of amoxicillin/clavulanate after completion of treatment. The authors concluded that azithromycin is comparable to amoxicillin/clavulanate to treat otitis media in children, and it is safer and more tolerable.

Guideline recommendations

Acute otitis media is usually a self-limiting disease and resolves spontaneously within two to seven days in 78% of cases. In paediatric patients without risk factors with uncomplicated acute otitis media, initial observation and symptomatic treatment with systemic analgesics should be carried out first; immediate antibiotic therapy should be avoided due to the rapidly growing resistance caused by antibiotic misuse, which is dependent on age, the severity of the patient's case, and ability to access healthcare facilities. The immediate administration of antibiotics has no effect on pain within the first 24 hours. The benefit of antibiotics has only been proven to a small extent with regard to pain from the 2nd day of treatment. Even in the case of fever and/or vomiting, it is justifiable to wait for the first 24-48 hours while observing the child and only prescribe antibiotics if the symptoms worsen or fail to improve. However, if earache persists after 48 hours and in patients with an increased risk (AOM with otorrhoea, aged less than 24 months with bilateral AOM, concomitant/underlying diseases, recurrent infections, tympanostomy tubes, immunosuppression, poor general condition, high fever, persistent vomiting and/or diarrhoea), immediate antibiotic therapy should be initiated. The following antibiotic therapy is overall recommended in guidelines as shown in a systematic review of 17 European national clinical practice guidelines for acute otitis media (AOM) in children (Suzuki et al 2020): Amoxicillin is considered the first-line treatment, and amoxicillin with clavulanic acid is encouraged to broaden antimicrobial coverage for patients with recurrent AOM and recent history of amoxicillin use in the previous month. Cephalosporin is used for patients with penicillin allergies, and macrolides are used if the patient is allergic to penicillin and cephalosporin. If symptoms persist after two to three days of proper antibiotic administration, diagnosis reassessment is considered, and a confirmed diagnosis without symptom improvement suggests treatment failure, which is first aided by an empiric broadening of antibiotic coverage; further treatment failure requires antibiotic susceptibility testing as determined by middle ear fluid cultures obtained by tympanocentesis.

AOM in adults

The incidence of acute otitis media (AOM) is much higher in children than in adults and therefore, most of the medical literature focuses on the diagnosis, treatment and complications of acute otitis media in children. Many of the data on acute otitis media in adults have been obtained and are extrapolated from studies in paediatric patients. There is limited data on the incidence of AOM in adults. A Dutch study (Rijk et al. 2021) examined the incidence in primary care and the current treatment of AOM in adolescents and adults aged 15 years and older between 2015 and 2018 (equivalent to a total of 1,261,575 person-years): 5,358 patients had one or more episodes of AOM (total number of AOM episodes: 6667; an average of 1.2 per patient). The overall incidence of AOM was 5.3/1000 person-years and was relatively stable over the study period. The incidence decreased with increasing age (from 7.1 in patients aged 15 to 39 years to 2.7/1000 person-years in patients aged 64 years and older).

Most of the data on the microbiology of acute otitis media were obtained by culturing middle ear fluid obtained by needle aspiration (myringotomy) in children. However, limited data show that the microbiology of acute otitis media in adults is similar to that in children: As in children, the most common pathogens are *Streptococcus pneumoniae Haemophilus influenzae* and *Moraxella catarrhalis* is the third most common otopathogen. While AOM caused by *S. aureus* (including methicillin-resistant strains) is rare in children, it is possibly more common as a cause of AOM in adults; however, the actual incidence is unknown.

In adults, dysfunction of the Eustachian tube, entities causing compression of the Eustachian tube or outlet obstruction or an abnormality in the host immunological response may predispose the individual to developing AOM. Further, the onset of AOM is often preceded by an upper respiratory tract infection or an exacerbation of seasonal allergic rhinitis. AOM in adults usually occurs on one side and is

characterised by earache and reduced or muffled hearing. Other symptoms such as high fever, severe pain behind the ear or facial paralysis indicate a rare complication.

Results of clinical studies in which adults with AOM were also included and which examined the efficacy and safety of azithromycin in the relevant indication and population do not allow for any valid conclusions to be drawn about how effective and safe azithromycin is specifically for the treatment of AOM in adults because of a lack of subgroup analyses related to the adult population. The studies are therefore to be considered primarily supportive.

In the scientific literature, only very limited data can be found regarding the effective and safe treatment of AOM in adults (Müller 1993, Müller 1996, O'Doherty 1996). Overall, the data from these few publications support the results from clinical trials and the scientific literature in children with AOM and suggest that azithromycin may be a treatment option for adults with AOM.

No EU/EEA treatment guidelines addressing the treatment of AOM in adults were identified.

Recurrent AOM

Recurrent AOM was not specified as part of the authorised indications. Recurrent AOM is usually defined in the scientific literature as ≥3 distinct and well-documented episodes of AOM within six months or ≥4 episodes within 12 months (Pichichero 2016). Winter season, male gender, prolonged use of pacifiers and passive exposure to smoking have been associated with an increased likelihood of recurrence. Predisposing factors also include underlying conditions such as cleft palate, syndromes with craniofacial anomalies including Down syndrome, and persistent Eustachian tube dysfunction. In addition, infants and toddlers whose first episode of AOM occurred before the age of six months are at higher risk for recurrent AOM. It is reported that half of children younger than 2 years treated for AOM will experience a recurrence within 6 months. Symptoms that last more than 10 days may also predict recurrence (Lieberthal, Carroll et al. 2013).

Interventional treatment options include watchful waiting with episodic antimicrobial therapy (particularly suitable for children ≥2 years of age because frequency of recurrent episodes declines with immunologic and physiologic maturation) or intensified treatment with prolonged antibiotic therapy or surgery with insertion of a ventilation tube, alone or in combination with adenoidectomy (Hoberman, Preciado et al. 2021).

Only limited data are available overall for recurrent AOM. A monocentre, open, comparative, perspective, randomised study was conducted (AZM-1-92-004 (completed 1996)) comparing azithromycin once weekly administration compared to amoxicillin daily over a course of 6 months. The result of the efficacy parameter (at least one relapse episode of otitis media) was slightly worse in the azithromycin treatment group after 24 weeks of treatment but comparable to amoxicillin treatment group after 48 weeks. No statistically significant differences were found at any time point. An open-label, comparative, randomised trial of azithromycin versus amoxicillin for prophylaxis in paediatric patients with recurrent otitis media was also conducted (AZM-AR- 96-001). However, due to the high dropout rate (58.14 %), no efficacy analyses could be performed.

In the scientific literature, only a few publications can be found that address the treatment of recurrent AOM with azithromycin. Mohs et al. (1993) report data from 13 cases of recurrent AOM (8 in the azithromycin group, 5 in the amoxicillin group). Arrieta et al. (2003) report data from a double-blind, double-dummy multicentre clinical trial in the US and Latin America comparing a high-dose azithromycin regimen with high-dose amoxicillin-clavulanate for the treatment of 300 children between 6 months and 6 years of age with recurrent or persistent AOM. The children were randomised to receive either high-dose azithromycin (20 mg/kg body weight once daily for 3 days) or high-dose amoxicillin-clavulanate (90 mg/kg divided twice daily for 10 days). Two-thirds of the patients were <2 years old. On days 12 to 16, the clinical success rates for azithromycin and amoxicillin-clavulanate

were comparable for all patients (86% vs. 84%) and for children <2 years (85% vs. 79%). On days 28 to 32, clinical success rates were higher for azithromycin than for amoxicillin-clavulanate in all patients (72% vs. 61%, P = 0.047) and in children under 2 years of age (68% vs. 51%, P = 0.017).

Azithromycin is not listed as a treatment option for patients with recurrent AOM in the current scientific literature.

Resistance development

Resistance data for *Streptococcus pneumoniae* and *Haemophilus influenzae* have been described in the section on LRTI above.

According to data from the SENTRY database, *Moraxella catarrhalis* is commonly susceptible to azithromycin, indicating low-level "category 1" resistance.

2.2.4. Acute bacterial skin and skin structure infections (ABSSSI) including folliculitis, cellulitis, erysipelas, impetigo and secondary purulent dermatitis

Uncomplicated skin and skin structure infections typically include cellulitis, folliculitis, impetigo, erysipelas and simple abscesses. These types of skin infections are most commonly caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. Less common causes include other *Streptococcus* species or Gram-negative bacteria.

In-vitro data indicate efficacy against *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus epidermidis*, however, the *in-vitro* activity is describes as considerably lower compared to erythromycin. Furthermore, *in-vitro* activity against some Gram-negative pathogens is described.

Clinical studies

The safety and effectiveness of azithromycin for treating skin and skin structure infections were initially evaluated in 5 comparative trials: one double-blind study (118) of azithromycin versus cephalexin and 4 randomised, comparative studies of azithromycin versus cephalexin (110), erythromycin stearate (304/304A), cloxacillin (316) or erythromycin ethylsuccinate (104). These studies showed comparable efficacy with the other antibiotics tested, while in study 316 azithromycin showed a significantly higher bacterial eradication rate in the azithromycin group compared to cloxacillin.

Jennings et al. (2003) investigated efficacy of azithromycin for the treatment of uncomplicated skin and skin structure infections in a multicentre, investigator blind study that compared the efficacy and safety of azithromycin with cefadroxil. A total of 296 patients were randomised to receive either azithromycin (500 mg ×1 day followed by 250 mg/day × 4 days) or cefadroxil (500 mg BID × 10 days). Clinical success rates assessed between days 28 and 32 were 100% for azithromycin and 90% for cefadroxil (p = 0.007). The eradication rates for *S. aureus* were 100% and 89%, respectively, and for *S. pyogenes* were 100% and 83%, respectively.

Guideline recommendations

According to WSES/GAIS/WSIS/SIS/AAST Recommendations for Management of SSTIs (2022), in CA-MRSA, if coverage for both streptococci and MRSA is desired, azithromycin is an alternative recommended in the case of beta-lactam allergy. Treatment of cat-scratch diseases includes azithromycin (500 mg on day 1, 250 mg/day for the next 4 days).

IDSA Clinical Practice Guidelines for SSTIs (2014) recommends azithromycin for cat scratch disease.

Resistance development

Regarding resistance development of *Staphylococcus aureus* the evidence suggests susceptibility rates over time against *S. aureus* have remained stable since 2018, with susceptibility rates around or higher than 70% reported in in the SENTRY (AZM resistance above 25% since 2019: 26.6% in 2021, 25.9% in 2022) and ATLAS databases (ERY data as surrogate; resistance level: 27.6% in 2018, 32.24% in 2021). In HR, methicillin-susceptible *S. aureus* (MSSA) strains show moderate rates of resistance to macrolides (17%) (Andrašević et al., 2022). Macrolide resistance remains the resistance most often associated with β-lactam resistance. In FR, among the β-lactam-resistant strains, 58% are macrolide-resistant (62% in children, 56% in adults) (Varon et al., 2021). Thus, Methicillin-resistant *S. aureus* (MRSA) is less likely to be susceptible to azithromycin than methicillin-susceptible strains of *S. aureus* (MSSA).

For *Streptococcus pyogenes* see indication URTI above.

2.2.5. Erythema migrans

Lyme disease (LD) is a systemic, tick-borne infection, caused by *Borrelia burgdorferi*. It is the most common tick-borne disease in Europe. The disease is divided into early and late stage. The most common sign of early stage is erythema chronicum migrans. Although erythema migrans is usually self-limited, untreated Lyme disease commonly disseminates, resulting in late stage with cardiological, neurological, joint and/or skin manifestations.

In vitro data indicate that azithromycin presents antibacterial activity against *Borrelia burgdorferi*.

Clinical studies

Clinical efficacy of azithromycin has been evaluated in patients with early Lyme disease. In the majority of adult studies azithromycin was administered in a total dose of 3 g (Pleterski-Rigler, 1993). Total dose in children was 60 mg/kg (Strle et al., 1992). With respect to resolution of signs and symptoms of early stage, and the prevention of late stage of Lyme disease, azithromycin was considered to be at least as effective as penicillin V and doxycycline (Weber et al 1993; Ruscio, 1996; Strle et al., 1996; Strle et al., 1993;). Moreover, in some studies, both erythema migrans and systemic symptoms of infection resolved more rapidly in azithromycin-, than in doxycycline-, or penicillin V-treated patients (Pleterski-Rigler, 1994; Gorišek and Rogl, 1996).

A randomised, multicentre, open clinical trial was undertaken to compare the efficacies of azithromycin (500 mg bid on the 1st day, followed by 500 mg once daily for the next 4 days) and doxycycline (100 mg bid for 14 days) in the treatment of patients with Lyme disease associated with erythema migrans. Clinical success was observed in 95.5% patients treated with azithromycin, and 82.5% patients treated with doxycycline (p=0.0731) (Baršić et al 2000).

A network meta-analysis evaluated efficacy and safety of antibiotic therapy in early cutaneous Lyme borreliosis in adult patients. Overall, 19 studies (2532 patients) were included. The antibiotics investigated were doxycycline, cefuroxime axetil, ceftriaxone, amoxicillin, azithromycin, penicillin V, and minocycline. Pooled effect sizes from NMAs did not detect any significant differences in treatment response by antibiotic agent, dose, or duration. There were also no differences in the effect sizes among antibiotic agents and treatment modalities in treatment-related adverse outcomes, which were generally mild to moderate, and treatment failures were rare (Torbahn et al. 2018).

A unblinded prospective clinical study was performed in patients younger than 15 years with untreated solitary erythema migrans referred to the institution during 2002–2003. Eighty-four patients received azithromycin (20 mg/kg/d (maximum, 1000 mg/d) for the first day followed by 10 mg/kg/d (maximum, 500 mg) in 1 daily dose for 4 additional days) and 84 amoxicillin (50 mg/kg/d (maximum,

1500 mg/d), divided into 3 equal doses, administered every 8 hours for 14 days). Comparison of azithromycin and amoxicillin for the treatment of children with solitary erythema migrans revealed comparable efficacy and adverse effects of treatment (Arnež & Ružić-Sabljić 2015).

A further study reported the results from the randomised, comparative study conducted in 93 patients (younger than 8 years were excluded) with clinically defined erythema migrans. Forty-nine of them were treated with doxycycline (100 mg twice daily for 14 days) and forty-four received azithromycin (500 mg twice daily for the first day, followed by 500 mg once daily for the next four days). Compared to doxycycline, azithromycin possessed equal efficacy for treatment of early Lyme borreliosis. (Christova & Komitova 2003).

Two further studies were identified that applied a 10-day azithromycin dose regimen (Strle et al 1992 (250 mg bd for two days followed by 250 mg od for eight days) and Weber et al 1993 (500 mg daily for 10 days). Azithromycin showed similar efficacy and safety to penicillin (in both studies) and doxycycline (in Strle et al 1992).

Guideline recommendations

According to the NICE guideline for Lyme disease treatment, oral azithromycin is recommended as second alternative in adults and young people (aged 12 and over) with Lyme disease without focal symptoms but with erythema migrans and/or non-focal symptoms (NICE NG95 2018).

The Clinical Practice Guidelines by the Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology for the Prevention, Diagnosis, and Treatment of Lyme disease recommends, for patients with erythema migrans, using oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil. For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin (Lantos et al., 2021). This is in line with the recommendations in the German AWMF S2k Guideline Cutaneous Lyme borreliosis.

In addition, according to the treatment guideline "Cutaneous Lyme borreliosis: Guideline of the German Dermatology Society" azithromycin is recommended in adults and children in the treatment of cutaneous Lyme borreliosis as an alternative treatment with the treatment duration of 5 – 10 days. The recommended dose for adults is 250 mg twice daily and for children 5-10 mg/kg/day.

Resistance development

Data on antibiotic susceptibility testing in *Borrelia burgdorferi* in general is scarce. Yet, no cases of acquired antibiotic resistance in *Borrelia burgdorferi* were reported. However, antibiotic tolerance/persistence of *Borrelia burgdorferi* in patients has been reported as reason of concern.

2.2.6. Dental infections (periodontal abscesses and periodontitis)

Since dental infection includes a vast number of different entities, a further specification of indications was deemed necessary. The following assessment focusses on the two indications periodontal abscesses and periodontitis already approved in some SmPCs.

Periodontal abscesses are a common and painful dental emergency resulting from bacterial accumulation or foreign body impaction in periodontal pockets. They affect both patients with or without active periodontal disease and require prompt as well as long-term management.

Periodontitis is a progressive multifactorial inflammatory disease associated with dysbiotic dental plaque biofilms of the tooth-supporting apparatus. Its primary features include the loss of periodontal tissue and alveolar bone loss, presence of periodontal pocketing and gingival bleeding. If untreated, it may lead to tooth loss, although it is preventable and treatable in the majority of cases.

The bacterial flora of odontogenic infections represents a mixed flora, in which both aerobic, facultative anaerobic as well as strictly anaerobic bacteria can be detected. The most frequently detected aerobic bacteria of odontogenic infections include the *viridans streptococci* and *Staphylococcus aureus*, but also *Neisseria* species, *Klebsiella* species, *Enterococcus faecalis*, *Capnocytophaga gingivalis*, *Actinobacillus actinomycetemcomitans, Eikenella corrodens* and *Lactobacillus* species. Among the anaerobic bacteria, *Peptostreptococcus* and *Prevotella* species dominate alongside *Porphyromonas* species. *Bacteroides* and *Fusobacterium* species can be detected alongside *Veillonella* and *Eubacterium* species as well as *Campylobacter* species.

The spectrum of *in-vitro* activity of azithromycin includes the following pathogens relevant for the indications periodontal abscesses and periodontitis: group A streptococci*, Staphylococcus aureus, Neisseria species* and *Peptostreptococcus*.

Clinical studies

Pfizer provided information on one pivotal clinical study. Study AZM-F-93-006 was a multicentre, double-blind study of the efficacy and safety of azithromycin (3 days) versus a spiramycin-metronidazole combination (7 days) in the treatment of stomatological infections of dental origin conducted in 1994-1997. The following efficacy results were reported:

Table 3: Response rates with 90% confidence interval limits, PP analysis

	AZM response rate	Comparator response rate	Rate diff	Lower limit (CI 90 %)	Upper limit (CI 90 %)
Ratio < 0.7	85.0 % (n=112/132)	92.3 % (n=130/141)	- 7.3 %	-13.6 %	-1.0 %
Ratio ≤ 0.3	60.2 % (n=79/132)	59.9 % (n=84/141)	0.3 %	-9.3 %	10.0 %

Table 4: Response rates with 90% confidence interval limits, ITT analysis

	AZM response rate	Comparator response rate	Rate diff	Lower limit (CI 90 %)	Upper limit (CI 90 %)
Ratio < 0.7	84.9 % (n=124/146)	92.7 % (n=139/141)	- 7.7 %	-13.7 %	-1.7 %
Ratio ≤ 0.3	59.6 % (n=87/146)	61.3 % (n=92/150)	-1.7 %	-11.1 %	7.6 %

The supportive studies AZM-B-95-001 (open, randomised clinical trial comparing the safety, tolerance and efficacy of azithromycin and amoxicillin/clavulanic acid in the treatment of acute periapical abscesses, 1996) and AZM-E-94-001 (open comparative multicentre study of the efficacy, safety and tolerance of azithromycin versus amoxicillin/clavulanic acid in the treatment of patients with dental and periodontal soft tissue infections, 1995-1997) were provided. Azithromycin was prescribed for 3 days, by oral route at 500 mg daily and was found to be as efficacious as amoxicillin/clavulanic acid in these infections.

Muniz et al. (2013), Teughels et al. (2020) and Keestra (2014) performed systemic reviews to determine the efficacy of azithromycin as treatment of periodontitis (alone and in combination, or in combination with scaling and root planning (SRP)). Most studies used azithromycin as an adjuvant treatment for chronic periodontitis, usually in a single daily dose of 500 mg for 3 days, and both reviews found that:

- the use of azithromycin as adjuvant to conventional treatment for chronic and aggressive periodontitis generally improves clinical and microbiological findings compared to conventional treatment alone and
- the best outcomes were observed for the combination of amoxicillin plus metronidazole, followed by metronidazole alone and azithromycin.

- systemic antibiotics combined with SRP offer additional clinical improvements compared to SRP alone. Although there were no statistically significant differences, there was a trend that for initially moderate and deep pockets, metronidazole or metronidazole combined with amoxicillin, resulted in clinical improvements that were more pronounced over doxycycline or azithromycin.

Guideline recommendations

In general, antibiotic treatment of odontogenic infections should only be considered in patients with a tendency to spread and or at risk for complications. According to the European Society of Endodontology Position Statement on the use of Antibiotics in Endodontics (2018), azithromycin should be used in case of penicillin allergy for adjunctive systemic treatment in conjunction with endodontic therapy. These recommendations are in line with other international and national guidelines (AWMF odontogenic infection GL and Belgian GL and American Dental Association GL, Sanz M. et al. 2008; AFSSAPS Recommendations 2011).

Resistance development

Because of the diversity of the flora of the oral cavity and the polymicrobial nature of dental infections, creating a concise list of pathogens relevant to the indication "dental infections" is difficult. Based on literature, *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Bacteroides* spp., *Fusobacterium* spp., *Porphyromonas gingivalis*, *Prevotella* spp., *Tannerella forsythia* and *Treponema denticola* were identified as major contributors to periodontal disease in humans.

According to Kuriyama et al. (2007), who determined the antimicrobial susceptibility of 800 isolates from patients with dentoalveolar infection, *Peptostreptococcus micros* and *Porphyromonas* species exhibited high susceptibility to azithromycin, while the majority of *Fusobacterium* strains were resistant to erythromycin and azithromycin. High erythromycin resistance rates in *Fusobacterium nucleatum* was also found in isolates from patients with endodontic infections, as well as high azithromycin-resistance (60%) in *Enterococcus faecalis*, which showed a medium erythromycin resistance rate (10%-20%) Ardila et al. (2023). Arrendondo et al. (2019) evaluated resistance to azithromycin and erythromycin of 100 *Prevotella* spp. isolates from 52 patients with chronic periodontitis. A higher degree of resistance to azithromycin and erythromycin was detected in comparison to previous studies, with a prevalence of 51% for *erm*(F) and 19% for *erm*(B). This is in accordance with the data of Ardila and Bedoya-García (2022), who assessed the prevalence and proportions of antimicrobial-resistant species in patients with odontogenic infections and found erythromycin-resistance in *Peptostreptococcus* spp., *Bacteroides* spp., and *Prevotella* spp., and azithromycin- and erythromycin-resistance in Gram-negative microorganisms.

2.2.7. Moderate acne vulgaris

Acne vulgaris is a common chronic skin disease involving blockage and/or inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous gland). Acne can present as non-inflammatory lesions, inflammatory lesions, or a mixture of both, affecting mostly the face but also the back and chest. Acne develops from the following four factors: (1) follicular epidermal hyperproliferation with subsequent plugging of the follicle, (2) excess sebum production, (3) the presence and activity of the commensal bacteria *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and (4) inflammation. In addition, genetics is also a key factor in the pathophysiology of acne (Rao et al., 2020).

Clinical studies

As stated by the MAH Teva B.V., azithromycin was investigated in a pilot study in 120 subjects to identify the optimum azithromycin dose in the treatment of acne vulgaris (Study SUM-OD-03-99-HR-1) in which subjects were randomised to one of the three treatment groups (A, total dose 4.5 g of azithromycin in 7 weeks; B, total dose 6.0 g in 10 weeks; and C, total dose 7.5 g in 13 weeks). The group percentage of "cure" was lower and group percentage of "treatment failure" higher in group A than in groups B and C. Authors concluded that azithromycin in a total dose of 6.0 g in 10 weeks seemed to be a promising agent in the treatment of papulopustular acne vulgaris with few side effects and good patient compliance (Basta-Juzbasic et al., 2007).

Based on results of this pilot study, 10 weeks of pulse azithromycin treatment with total dose of 6 g of azithromycin was selected to be compared with doxycycline as standard tetracyclines treatment of moderate acne vulgaris in a double-blind, controlled, prospective study in 240 patients. Reduction in the number of lesions was similar with both azithromycin and doxycycline treatments. Also, the upper 95% confidence limit of 5 inflammatory lesions has satisfied the noninferiority criterion (Maleszka et al., 2011; SUM-AD-03-02-INT-1).

In a randomised, comparative study the role of a monthly dose of azithromycin was evaluated and compared with daily doxycycline treatment (Parsad et al., 2001). Sixty patients with moderate to severe acne were randomly assigned to two treatment groups, azithromycin, and doxycycline, both in combination with tretinoin cream 0.05 %. The monthly dose of azithromycin was found to be as effective as daily doxycycline on a pure protocol basis and statistically significantly better than doxycycline by intention to treat analysis.

Another dosing scheme was presented in a small (n=51) randomised, investigator-blinded study that was performed in order to compare the efficacy of azithromycin (500 mg/day on 3 consecutive days per week in the first month, on 2 consecutive days per week in the second month, and on 1 day per week in the third month) with doxycycline (twice a day for the first month and once a day for the second and third months). Statistically significant improvement for the facial lesions was obtained with both drugs. However, no statistically significant difference was found for efficacy parameter between two treatment groups. The beneficial effect continued until two months after treatment (Kus et al., 2005).

A meta-analysis of randomised controlled trials included six studies assessing 906 patients with moderate to severe acne vulgaris. Results revealed no significant difference between the two groups regarding remaining acne lesion counts (p=0.27), patients' self-assessment of treatment (p=0.67), and the investigators' assessment of treatment (p=0.32). The authors concluded that azithromycin pulse therapy is equivalent to doxycycline at 12 weeks in the efficacy of the treatment for moderate to severe acne vulgaris and that oral azithromycin pulse therapy may be an alternative to doxycycline in the management of acne for those unable to tolerate doxycycline (Kim et al., 2018).

Guideline recommendations

According to the last international consensus from the Global Alliance to Improve Outcomes in Acne (2018), retinoids have an essential role in the treatment of acne. For most patients with inflammatory acne, comedonal acne, or both, a topical retinoid plus benzoyl peroxide (BPO) is recommended as first-line therapy. Together, these agents target multiple aspects of acne pathophysiology, working to normalize keratinization, reduce inflammation, and kill *P. acne*. The same consensus acknowledges that the role of antibiotics in acne therapy has changed. Neither topical nor systemic antibiotics should be used as monotherapy for acne treatment. Systemic antibiotics are useful for moderate-to-moderately severe acne, but efforts should be made to limit the duration of therapy to 3-4 months. The top 3 factors to consider when determining duration of antibiotic therapy include the severity of

acne, the potential for bacterial resistance, and the response to treatment. Factors that make it difficult to limit the duration of systemic antibiotic therapy include acne recurrence and patient preference. Oral antibiotics are indicated when inflammatory acne is not responding well to topical treatments and acne involving trunk or multiple bodily areas. Response to therapy should be evaluated at 6-8 weeks (Thiboutot et al 2018).

Resistance development

According to a review by Karadag et al. (2021), resistance for the newer macrolides like azithromycin and clarithromycin has been increasing in *Cutibacterium acnes*. Azithromycin showed regionally variable resistance rates according to publications from 2010 to 2020 in non-European countries, which ranged from 5% (Egypt) to 100% (India).

Recent European data on azithromycin resistance in *C. acnes* is scarce. Mercieca et al. (2020) isolated *C. acnes* strains from patients in Malta between December 2015 and September 2017. Azithromycin-resistance was found in 18% of isolates.

2.2.8. Sexually transmitted diseases (urethritis, cervicitis, prostatitis, chancroid)

Urethritis/cervicitis due to Chlamydia trachomatis

Chlamydia trachomatis is the most common bacterial cause of sexually transmitted disease and is a serious international health issue (Topic et al., 2006, Geisler, 2007, Gerbase et al., 1998). *Chlamydia trachomatis* affects all age groups, with the greatest risk in individuals <25, and can cause acute and chronic, recurrent and persistent urogenital infections. Asymptomatic infection is common in both men and women and detection frequently relies on screening. The most common manifestation of disease is local mucosal inflammation associated with a discharge, urethritis in males and urethritis/vaginitis/cervicitis in female patients. Complications in women can include pelvic inflammatory disease, ectopic pregnancy, neonatal transmission, and infertility and in men epididymitis and prostatitis. Both men and women can also develop rectal infections, conjunctivitis and Reiter's syndrome.

In vitro azithromycin presents antibacterial activity against *Chlamydia trachomatis,* a strict intracellular pathogen. After oral administration, azithromycin distributes to the extravascular compartment, reaching initially high intracellular and tissue concentrations.

Clinical studies

As documented by the originator, clinical trial documentation for the treatment of chlamydial urethritis/cervicitis initially comprised 6 studies investigated between 1986 and 1988 (studies 101, 107A, 119, 301A/B, 320 and 125) in which 674 patients aged 16 or older received azithromycin. Most of the trials compared 1-day treatment with azithromycin versus multiple doses of the comparative agent (studies 101, 107A, and 301A/B). In addition to having a 1-day azithromycin treatment group, Protocols 101, 107A, and 301A/B, also had a 3-day regimen group. All studies used a total dose of 1 g of azithromycin. These studies demonstrated that a single 1 g dose of azithromycin was as safe and effective in the treatment of chlamydial urethritis/cervicitis as a standard 7-day regimen of doxycycline. Bacterial eradication was seen in 293/305 (96.1%) evaluable azithromycin patients (1 g single dose) and 253/257 (98.4%) evaluable doxycycline patients at last evaluation.

Literature data included randomised clinical trials in which azithromycin was compared to doxycycline for chlamydial infections. These trials found a single dose (1 g or 3 g) azithromycin to be equivalent to standard therapy with doxycycline in terms of bacteriologic cure (Martin et al., 1992), pathogen eradication (Topic et al., 2006, Thorpe et al., 1996) or treatment failure (Geisler et al., 2015).

The Cochrane Database of Systematic Reviews investigated interventions for treating genital Chlamydia trachomatis infection in pregnancy. Eight comparisons were included in this review; three compared antibiotics (erythromycin, clindamycin, amoxicillin) versus placebo; five compared an antibiotic versus another antibiotic (erythromycin, clindamycin, amoxicillin, azithromycin). No study reported different antibiotic regimens. Treatment with antibacterial agents achieves microbiological cure from *Chlamydia trachomatis* infection during pregnancy. There was no apparent difference between assessed agents (amoxicillin, erythromycin, clindamycin, azithromycin) in terms of efficacy (microbiological cure and repeat infection) and pregnancy complications (preterm birth, preterm rupture of membranes, low birth weight). Azithromycin and clindamycin appear to result in fewer side effects than erythromycin. All the studies in this review were conducted in North America, which may limit the generalisability of the results. In addition, study populations may differ in low-resource settings and these results are therefore only applicable to well-resourced settings. Furthermore, the trials in this review mainly took place in the nineties and early 2000's and antibiotic resistance may have changed since then (Cluver et al., 2017).

Guideline recommendations

In the European Guideline on the Management of Chlamydia Trachomatis (2015), azithromycin (oral, 1 g) is a recommended first-line treatment option. Especially in pregnancy and during breast feeding and for acute or chronic follicular conjunctivitis. In the CDC Sexually Transmitted Infections Treatment Guidelines (2021), doxycycline (100 mg orally 2 times/day for 7 days) or as alternative regimens azithromycin (1 g orally in a single dose), or levofloxacin (500 mg orally once daily for 7 days) are recommended regimen for chlamydial infection among adolescents and adults.

Resistance development

Resistance data provided indicate a common susceptibility of azithromycin against *Chlamydia trachomatis*.

Prostatitis caused by *Chlamydia trachomatis*

Chlamydia trachomatis can cause chronic bacterial prostatitis. Even if more than 50% of men with *Chlamydia trachomatis* infections are asymptomatic, acute manifestation of the infection is responsible for a number of symptoms, infertility, and long term reduced quality of life.

In vitro azithromycin presents antibacterial activity against *Chlamydia trachomatis,* a strict intracellular pathogen. After oral administration, azithromycin distributes to the extravascular compartment, initially reaching high intracellular and tissue concentrations.

Clinical studies

A chronic prostatitis study comparing azithromycin with clarithromycin (Škerk et al., 2002, Škerk et al., 2003) found similar eradication and clinical cure rates for both drugs. When compared to ciprofloxacin significantly higher clinical cure was achieved in the group of patients treated with azithromycin. A study by the same author in 2004 comparing a 4.5 g dose (given as a 3-day therapy of 1 x 500 mg weekly for 3 weeks (46 patients)) with 6.0-g dose (given as a 3-day therapy of 1 x 500 mg for 4 weeks (43 patients)) found that eradication rate and clinical cure did not significantly differ with regards to the total dose of 4.5g or 6.0 g of azithromycin administered.

Another study from Škerk et al. in 2004, involving 125 patients, compared azithromycin (4.0 g given as a single dose of 1 × 1000 mg weekly for 4 weeks) with doxycycline (100 mg b.i.d. for 28 days) found no significant difference between the eradication rates and the clinical cure rates of the two antimicrobials.

Guideline recommendations

The Guidelines on urological infections of the European Association of Urology and 2015 European *Chlamydia trachomatis* guideline recommend both azithromycin and doxycycline as first-line treatment for chronic bacterial prostatitis caused by *Chlamydia trachomatis*.

Resistance development

Resistance data provided indicate a common susceptibility of azithromycin against *Chlamydia trachomatis*.

Urethritis/cervicitis due to Neisseria gonorrhoeae

Infection with *Neisseria gonorrhoeae* is an important cause of cervicitis, urethritis, and pelvic inflammatory disease (Newman et al., 2007). Gonorrhoea is the second most commonly reported bacterial STD. The majority of urethral infections caused by *Neisseria gonorrhoeae* among men produce symptoms that cause them to seek curative treatment soon enough to prevent serious sequelae, but treatment might not be soon enough to prevent transmission to others. Among women, infections often do not produce recognisable symptoms until complications (e.g. PID) have occurred. Both symptomatic and asymptomatic cases of PID can result in tubal scarring that can lead to infertility or ectopic pregnancy. The selection of appropriate therapy for gonorrhoea is complicated by the ability of *Neisseria gonorrhoeae* to develop resistance to antimicrobial therapies and the incidence of resistance varies with the geographical area.

In-vitro activity of azithromycin includes efficacy against *Neisseria gonorrhoeae* and high tissue concentrations are reached when using oral azithromycin.

Clinical studies

The clinical trial documentation for the treatment of gonococcal urethritis/cervicitis initially comprised 5 studies investigated between 1988 and 1990 (114, 124, 130, 305 and 319) in which 589 patients aged 16 or older received azithromycin. Of the 3 studies conducted in the US, two (114, 130) were open-label, randomised, comparative trials of azithromycin versus ceftriaxone and one (124) was an open-label, non-comparative trial. The results of these 3 studies support the conclusion that azithromycin is effective as a single oral 2 g dose for the treatment of acute gonococcal urethritis/cervicitis. In addition to these 3 studies, the results of 2 non-US studies (305, 319) provide additional safety data for this indication.

In two further trials published in the literature a single 1 g dose (Swanston et al.,2001) and a single 2 g dose (Takahashi et al.,2014) were effective for patients with gonococcal and nongonococcal urethritis in terms of improvement of clinical signs and symptoms and bacterial eradication.

Guideline recommendations

The European Guideline on Diagnosis and Treatment of Gonorrhoea in Adults (2020) recommends high-dose ceftriaxone and azithromycin (ceftriaxone 1 g plus azithromycin 2 g) or ceftriaxone 1 g monotherapy for uncomplicated gonorrhoea infections when the antimicrobial susceptibility is unknown. Azithromycin is also used in combination with ceftriaxone for gonococcal infections in pregnancy or when breastfeeding, for gonococcal infection of the pharynx and for gonococcal conjunctivitis. It is used in combination with spectinomycin or gentamicin when ceftriaxone resistance is identified. The German AWMF S2k guideline Diagnosis and Therapy of Gonorrhoea recommends empiric treatment with ceftriaxone 1-2 g IV or IM plus 1.5 g oral azithromycin (both as single doses).

However, regarding guidelines outside of EU/EEA, it is noted that in the update of the new CDC guidance, co-treatment for gonorrhoea with azithromycin is no longer recommended.

Resistance development

The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) reports on resistance in *Neisseria gonorrhoeae* against azithromycin. In 2022, around 25.6% of isolates had an MIC >1 mg/L (EUCAST ECCOFF), which was a significant increase since 2019 (ECDC, Euro-GASP, 2021). Isolates with an azithromycin MIC above the ECOFF were collected in the 23 EU/EEA countries that participated in Euro-GASP. Thirteen isolates displayed 'high-level azithromycin resistance' with MICs of ≥256 mg/L compared to 19 in 2021. Of the 13 high-level azithromycin-resistant isolates, one was also resistant to ceftriaxone (MIC=0.25 mg/L), cefixime (MIC=1 mg/L) and ciprofloxacin.

On a national level, common susceptibility of *Neisseria gonorrhoeae* towards azithromycin (resistance rate <10%) was seen in FR (9%, 2022), PT (average 5.04% between 2003 and 2018, always below 10%), and DK (2% in 2020), while commonly acquired resistance was described in DE (12.2% in 2020, preliminary 20.7% in 2021), SE (34% in 2021), AT (19.6% in 2021), BE (33.6% in 2022), FI (16% in 2020), and IE (11% in 2021). Lu et al. (2022) conducted a meta-analysis of 134 reports from 51 countries, covering 165,172 *Neisseria gonorrhoeae* isolates and found a global prevalence of resistance over the past three decades of 6% for azithromycin and 48% for erythromycin with a significant change in macrolide resistance prevalence over time. Since azithromycin-resistance in *Neisseria gonorrhoeae* in the EU/EEA is increasing, but resistance rates on the EU level did not exceed the 10% threshold, proper surveillance and resistance testing of this organism is especially important.

Urethritis and cervicitis caused by *Mycoplasma genitalium*

While urethritis and cervicitis due to *Mycoplasma genitalium* was not specifically mentioned in the indications, it could be considered part of a broad indication included in SmPCs of some azithromycin products in the form of "*mycoplasmosis*" stated in the context of sexually transmitted diseases.

Since *Mycoplasma genitalium* lacks a bacterial wall, it is intrinsically resistant to various antibiotics classes such as beta-lactams. Active classes include tetracyclines, macrolides, quinolones and streptogramines. Therapy for *Mycoplasma genitalium* is indicated if *Mycoplasma genitalium* is detected. This is intended to prevent sexual transmission and later complications such as PID and negative reproductive outcomes. Current partners of *Mycoplasma genitalium*-positive patients should be tested and treated with the same antimicrobial as the index patient. A test of cure should be considered in all patients.

Clinical data

Some of the trials discussed in the section on urethritis/cervicitis due to *Neisseria gonorrhoeae* also included patients with *Mycoplasma genitalium* infection, e.g. Takahashi (2014) found a microbiological eradication rate of 71.4% for *Mycoplasma genitalium* in male urethritis patients.

In the current European guideline on the management of *Mycoplasma genitalium* infections (Jensen et al., 2021), azithromycin is included as first-line therapy for the treatment of uncomplicated *Mycoplasma genitalium* infection without macrolide resistance mutations or resistance testing. The regimen recommended is azithromycin 500 mg on day one, followed by 250 mg on days 2–5 (oral, total dose: 1.5 g). This regimen is also effective for the treatment of *Chlamydia trachomatis* uncomplicated infections. The extensive use of 1 g single dose azithromycin globally for sexually transmitted diseases, in particular for uncomplicated infections due to *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Neisseria gonorrhoeae* (the latter, in combination with ceftriaxone) are likely to have contributed to the accelerated selection of macrolide-resistant strains in *Mycoplasma genitalium*.

Due to the observation that cure rates with azithromycin were lower for high-load infections, the concept of resistance-guided sequential therapy (RGST) has been developed. A seven-day course of

doxycycline substantially reduces organism load in most cases of *Mycoplasma genitalium* infection, but it results in microbiologic cure in only 30 to 40 % of the patients. Therefore, after the initial treatment with doxycycline (7 days), the patients are subsequently treated with a 2.5 g oral dose of azithromycin (1 g on day 1 followed by 500 mg days 2–4).

This form of RGST is now the recommended treatment in the Australian *Mycoplasma genitalium* guidelines and the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Infections Treatment Guideline (2021) for macrolide-sensitive *Mycoplasma genitalium* infections. A different regimen of RGST is recommended in the British Association for Sexual Health and HIV (BASHH) guidelines (2018, last updated: 2023): doxycycline 100 mg twice a day for seven days followed by azithromycin 1 g orally as a single dose then 500 mg orally once daily for 2 days (total azithromycin dose: 2 g) where the organism is known to be macrolide-sensitive or where resistance status is unknown.

Nonetheless, the European Guidelines (2021) highlight that there is no clinical evidence that the higher dose (2–2.5 g) of azithromycin is better than the 1.5 g extended dosage scheme previously recommended and that clinical trials, preferably randomised and controlled, evaluating this approach would be valuable.

Resistance development

A systematic review and meta-analysis described a marked increase globally in macrolide resistance from 10% before 2010 to 50% in 2016–2017. These results were updated up to February 2022 and it was found that compared with 2015–2017, global macrolide resistance was stable at 44.8% in 2018–2020, although in Europe, prevalence continued to increase (from 30% in 2015–2017 to 43% in 2018–2021). In those regions where stabilisation was apparent, plausible explanations include reduced use of single-dose azithromycin as first-line therapy and the uptake of resistance-guided therapy for *Mycoplasma genitalium*.

Chancroid due to *Haemophilus ducreyi*

Chancroid or ulcus molle is a sexually transmitted infectious disease that is rare in Europe and is caused by the bacterium *Haemophilus ducreyi*. It occurs mainly in tropical countries (e.g. Southeast Asia, Africa) but also in Latin America. The disease affects men about five times as often as women. The combination of a painful genital ulcer and tender suppurative inguinal adenopathy suggest the diagnosis of chancroid. A definitive diagnosis requires identification on special culture media or via PCR.

In vitro activity of azithromycin includes efficacy against *Haemophilus ducreyi* and high tissue concentrations are reached when using oral azithromycin.

Clinical trials

The clinical trial documentation of Pfizer for the treatment of genital ulcer disease due to *Haemophilus ducreyi* initially comprised 3 studies: 120, 328 and AZM-NY-90-007 investigated between 1989 and 1991 in which 258 patients aged 16 or older received azithromycin. The results supported the conclusion that a single 1 g oral dose of azithromycin is as effective as a single 250 mg intramuscular injection of ceftriaxone and oral erythromycin (500 mg QID for 7 days) in the treatment of genital ulcer disease caused by *Haemophilus ducreyi* in males. A single 1 g oral dose of azithromycin appeared to be as effective as a single 250 mg IM injection of ceftriaxone in the treatment of genital ulcer disease caused by *Haemophilus ducreyi* in females, but the number of female patients precluded definitive conclusions.

No additional publications were provided related to the indication chancroid due to *Haemophilus ducreyi* as part of this procedure.

Guideline recommendations

In the CDC Sexually Transmitted Infections Treatment Guidelines (2021), azithromycin (1 g orally in a single dose), or ceftriaxone (250 mg IM in a single dose), or ciprofloxacin (500 mg orally 2 times/day for 3 days), or erythromycin base (500 mg orally 3 times/day for 7 days) are the recommended regimens for chancroid.

Resistance development

Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported (Lautenschlager 2017). Nevertheless, there has been a lack of published antimicrobial susceptibility data for *Haemophilus ducreyi* for the past two decades. The absence of such data could be due to various reasons such as a decrease in the prevalence of the disease, difficulties in culturing the bacterium, or challenges in conducting and funding the necessary research (Lautenschlager et al., 2017). Global information on macrolide resistance in *Haemophilus ducreyi* is scarce but indicates high azithromycin susceptibility rates, and resistance data from Europe are actually not available. This might be especially attributable on the low incidence of *Haemophilus ducreyi* infection in Europe.

2.2.9. Pelvic inflammatory disease (PID)

PID is an infection of the female reproductive system including endometritis, salpingitis, oophoritis and pelvic peritonitis, which is caused by ascending infection from the vagina or the cervix. Typical symptoms include pelvic pain and vaginal discharge. Normally, oral treatment with appropriate antibiotics is sufficient, however, in severe cases, fever, severe pain and a pronounced feeling of illness occur where initial treatment with IV antibiotics is indicated. If left untreated, PID can lead to adhesions and resulting fertility problems in premenopausal woman.

In sexually active premenopausal women, a broad spectrum of bacteria are possible as causative pathogens. In addition to the sexually transmitted bacteria *Neisseria gonorrhoeae, Chlamydia trachomatis* and *Mycoplasma genitalium*, the vaginal flora and the pathogens of bacterial vaginosis (principally the anaerobes *Peptococcus* spp., *Peptostreptococcus* spp., *Bacteroides bivius*, *Bacteroides disiens* and *Bacteroides fragilis*) as well as in rare cases *mycoplasma* and *ureaplasma* can cause PID. Empiric antibiotic treatment includes a combination of antibiotics with broad efficacy against these pathogens.

The spectrum of *in-vitro* activity of azithromycin includes the following pathogens relevant for the indication PID: *Neisseria gonorrhoeae, Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis*. However, increased rates of resistance have been reported in some of them such as *Neisseria gonorrhoeae* and *Mycoplasma genitalium*. For this reason, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin.

Clinical studies

A clinical study report (dated January 2002) of a double blind, double dummy, randomised, multicentre, comparative study of the efficacy, safety and tolerability of oral azithromycin tablets versus oral ofloxacin and metronidazole in the treatment of patients with mild to moderate acute salpingitis (PID) was submitted. The study was investigated in the time period 1996-1998. Subjects were randomised into three treatment groups (oral azithromycin 500 mg once a day for 3 days; azithromycin 100 mg as a single dose on the first day followed by 500 mg once a day for 2 days; or oral ofloxacin 400 mg twice a day plus oral metronidazole 500 mg twice a day for 14 days). Satisfactory clinical response was documented in 76% (azithromycin 1500 mg group, n=50), 83%

(azithromycin 2000 mg group, n=46) and 88% (ofloxacin-metronidazole group, n=50) of treated patients.

Furthermore, information was provided about the two pivotal trials (Studies 341 and 342) which investigated IV azithromycin in the indication PID. These studies included only subjects appropriate for initial inpatient IV therapy. Three treatment groups were investigated: azithromycin 500 mg IV for one day (two days in study 342), followed by 250 mg oral daily for six days (five days in study 342); azithromycin (same dosage) plus metronidazole either 500 mg IV TDS for one day followed by 400/500 mg oral TDS for 11 days, or 400/500 mg oral TDS for 12 days; metronidazole (same dosage), with concomitant doxycycline (100 mg oral BD for 14 days) plus cefoxitin (2g IV or IM stat) and probenecid (1 g oral on Day 1) (study 341) or doxycycline (100 mg oral BD for 21 days) plus co-amoxiclav (1 g IV TDS for 5 days then 500 mg oral TDS for 16 days). The following efficacy results were reported:

Table 5: Pfizer studies supporting the PID claim, clinical outcome at end of treatment, evaluable subjects

Clinical response rates (%):	Azithromycin				Azithromycin plus Metronidazole				Comparator*			
	N	Cure	Imp	Fail	N	Cure	Imp	Fail	N	Cure	Imp	Fail
Laparoscopy at baseline	**33**	79	18	3	**31**	84	16	0	**26**	88	8	4
No laparoscopy at baseline	**6**	50	50	0	**9**	56	44	0	**3**	67	33	0
All subjects	**39**	74	23	3	**40**	78	23	0	**29**	86	10	3

Source: Efficacy Table 11.1.1
Key: Imp = Improved
*Comparator for Study 341 = metronidazole+doxycycline+cefoxitin+probencid
*Comparator for Study 342 = doxycycline + co-amoxiclav

In the literature Savaris et al. (2007) concluded that in this RCT 1 g of azithromycin weekly for 2 weeks combined with ceftriaxone is equivalent to ceftriaxone plus a 14-day course of doxycycline for treating mild PID. Bevan et al. (2003) found in a randomised open-label study that azithromycin, alone or with metronidazole, provides a shorter, simpler treatment option for the successful management of acute PID. In an unblinded, non-comparative phase 3 trial (Mikamo et al., 2014) the authors concluded that azithromycin intravenous-to-oral switch therapy demonstrated clinical and bacteriological effects for PID caused by various etiologic agents including quinolone-resistant strains.

Guideline recommendations

The recommended treatment for PID is based on published treatment guidelines and considers the severity of infection, clinical presentation, and an understanding of the polymicrobial nature of PID.

The European Guideline for the Management of PID (Ross et al., 2017) recommends treatment including ceftriaxone 500 mg IM single dose plus oral azithromycin 1 g single dose followed by a second dose of oral azithromycin 1 g after one week as an alternative treatment option. In the CDC Recommendation for treatment of PID (2021), treatment regimen of azithromycin 500 mg IV daily for 1–2 doses, followed by 250 mg orally daily for a total azithromycin duration of 7 days or in combination with metronidazole 500 mg 3 times/day for 12–14 days is recommended in case of cephalosporin allergy.

Anaerobic bacteria have been isolated from the upper genital tract of women who have PID, and data from *in vitro* studies have revealed that some anaerobes (e.g. *Bacteroides fragilis*) can cause tubal and epithelial destruction. Addition of metronidazole to IM or oral PID regimens more effectively eradicates anaerobic organisms from the upper genital tract and therefore most recent guidelines recommend the systematic use of it.

Resistance development

Resistance data for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are discussed above. As previously said, high resistance rates have been reported for *Mycoplasma genitalium*, the role of which in the pathogenesis of PID has evolved such that some studies have reported that *Mycoplasma genitalium* PID and cervicitis incidence rates are comparable to *Chlamydia trachomatis*.

Data on azithromycin resistance in *Ureaplasma* spp. is very limited and does not reflect all regions from the EU/EWR area. Resistance rates between 0 and 10% were measured, but the number of isolates was varying (DE: 170 strains, isolated 2016-2019, 0% resistance; EL: 2992 isolates, 2014-2022, 3.05-7.03%; PL: 141 isolates, 2003-2015, ~10%). From the available data, there were no concerns regarding high resistance rates in the genus *Ureaplasma*.

2.2.10. *Mycobacterium avium* complex (MAC) infection in people living with HIV

MAC can cause opportunistic infections in immunocompromised subjects. Disseminated MAC infection is a severe complication of advanced HIV/AIDS disease, which may lead to a pulmonary disease resembling tuberculosis (TB) in patients with lung disorders, including bronchiectasis, chronic obstructive pulmonary disease and pneumoconiosis or residual granulomatous lesions produced by TB and mycoses. DMAC infection is associated with significant morbidity and mortality in patients with AIDS and results in increased hospital admission and short survival. Treatment regimens include at least two effective antibiotics. Prophylaxis against non-tuberculous Mycobacteria may be considered in subjects with CD4 counts <50 cells/µL who remain viraemic on their antiretroviral regimen (ART).

Azithromycin shows good *in vitro* activity against pathogens of the *Mycobacterium avium* complex.

Prophylaxis of MAC infection in people living with HIV

Clinical studies

The Phase 3 program dated 1995 consisted of two randomised, double-blind, controlled clinical trials to investigate the efficacy of 1200 mg weekly azithromycin in the prevention of MAC and other opportunistic infections in subjects living with HIV with CD4 counts below 100 cells per mm^3. Azithromycin was shown to be statistically significantly superior to placebo as prophylaxis against disseminated MAC disease. Furthermore, azithromycin was at least as effective as rifabutin in this indication with a one-year incidence of 7.62% in the azithromycin group and 15.25% in the rifabutin group. The combination of azithromycin and rifabutin prevented disseminated MAC disease better than either of the drugs as monotherapy (one year incidence 2.75%).

Guideline recommendations

The European AIDS Clinical Society Guidelines (2023) recommend oral azithromycin 1200-1250 mg once weekly or clarithromycin 500 mg twice daily or rifabutin 300 mg once daily for MAC prophylaxis. In the WHO guideline "Management of Opportunistic Infections and General Symptoms of HIV/AIDS Clinical Protocol for the WHO European Region (2006)" azithromycin 1200 mg, PO QW is recommended as first-choice antibiotic. Alternative antibiotic is clarithromycin 500 mg PO BID.

Treatment of DMAC infection in people living with advanced HIV infection

Clinical studies

Overall, six clinical Phase 2 and 3 studies were investigated to support the indication "Treatment of DMAC infection in patients with advanced HIV infection" in 2000 (one pivotal study, two primary supportive studies and 3 additional studies designed as compassionate use with one of them in non-

disseminated disease). A total of 716 subjects were included in these six MAC treatment studies, of whom 630 subjects received azithromycin. The pivotal study was a multicentre, double blind, randomised comparison of single, oral, daily doses of azithromycin (250 mg or 600 mg) with clarithromycin 500 mg BID administered for 24 weeks in HIV-positive patients. In addition, both groups received a single daily dose of ethambutol (800 mg or 1200 mg based on body weight). The study demonstrated a comparable efficacy of azithromycin 600 mg once daily and clarithromycin 500 mg BID (both in combination with ethambutol) for the treatment of DMAC (bacteriological EP and clinical EP time to death).

Koletar et al. (1999) conducted a multicentre, randomised, dose-ranging study to determine the safety and efficacy of two different doses of azithromycin for treating DMAC in patients with AIDS. Azithromycin 600 or 1,200 mg daily for 6 weeks. This study demonstrates that azithromycin is useful as the primary macrolide in the treatment of DMAC. Symptomatic improvement and quantitative reduction in mycobacteraemia occurred with both 600- and 1,200-mg doses.

Guideline recommendations

In the European AIDS Clinical Society Guidelines (2023) azithromycin (500 mg qd po) plus ethambutol (15-20 mg/kg qd po) is a preferred therapy for treatment of MAC. In the ATS/ERS/ESCMID/IDSA Clinical Practice Guideline on Treatment of Nontuberculous Mycobacterial Pulmonary Disease (2020) recommends a 3-drug regimen that includes a macrolide over a 3-drug regimen without a macrolide in patients with macrolide-susceptible MAC pulmonary disease. Azithromycin-based treatment regimens are preferred over clarithromycin-based regimens because of better tolerance, less drug-interactions, lower pill burden (single daily dosing), and equal efficacy. However, when azithromycin is not available or not tolerated, clarithromycin is an acceptable alternative.

Resistance development

Loewenstein et al. (2023) retrieved patients with macrolide-resistant MAC isolates between March 2019 and March 2022 from the mycobacteriology reference laboratory database at Radboud UMC, Nijmegen, the Netherlands and identified sixteen patients with macrolide-resistant MAC disease in a total of 815 patients with MAC isolates (2%). Wetzstein et al. (2020) investigated phenotypic and genotypic antibiotic susceptibility patterns of 98 MAC isolates from a cohort from the metropolitan region of Frankfurt, Germany for the period 2006–2016. Here, according to CLSI breakpoints, macrolide resistance was rare (1.2% [95% CI 0.7–7.3]) in isolates in the base cohort. Wetzstein et al. (2024) performed whole genome sequencing (WGS) on a multi-national set of MAC 610 isolates from 465 patients from Germany, France, and Switzerland. Predicted resistance to macrolides was rare. Overall, 62/1917 isolates with known *rrl* mutations conferring macrolide resistance were found in the global dataset (3.2%).

Overall, limited data on azithromycin/macrolide resistance of species of the *Mycobacterium avium* complex is available. Nevertheless, the data summarized above indicates a low resistance rate of MAC species towards macrolide antibiotics.

2.2.11. Gastro-duodenal infections caused by *Helicobacter pylori*

This indication for orally administered azithromycin is only authorised in the MSs HR and SK.

Helicobacter pylori is the most prevalent chronic bacterial infection and is associated with peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

Most people become infected with *Helicobacter pylori* in the first few years of life without realising it. The bacterium can survive in the acidic environment of the stomach by producing an alkaline

protective layer. There it damages the mucous membrane and can cause inflammation. The exact mode of transmission of an *Helicobacter pylori* infection (oral-oral, gastral-oral, faecal-oral or their combination) is still unclear.

A systematic review with meta-analysis of the global prevalence of *Helicobacter pylori* infection shows a strong variation of infection between different regions and countries. According to current findings, the highest prevalence is in Africa (70.1%, 95%CI, 62.6-77.7) and the lowest in Oceania (24.4% 95%CI 18.5-30.4). At 34.3% (95%CI 31.3-37.2), Western European countries are among the regions with the lowest prevalence in a global comparison. However, the prevalence varies greatly within Europe, with the highest values in Portugal (86.4%), Estonia (82.5%) and Latvia (79.2%) and the lowest values in Switzerland (18.9%), Denmark (22.1%) and Sweden (26.2%).

Clinical studies

The indication for the treatment of "Stomach and duodenal infections caused by *Helicobacter pylori*" was granted for azithromycin-containing medicinal products based on a single study performed in 1997 (SUM-AD-05-97-HR-2). In this multicentre, randomised, parallel-group study, the efficacy and safety of a dual therapy of azithromycin and ranitidine bismuth citrate was compared with a triple therapy of azithromycin, amoxicillin and ranitidine bismuth citrate in the eradication of *Helicobacter pylori* in 144 patients with gastric ulcers. Overall, the study showed that triple therapy with azithromycin, amoxicillin and ranitidine bismuth citrate achieved a higher rate of eradication and clinical cure of *Helicobacter pylori* than a dual therapy with azithromycin and ranitidine bismuth citrate.

Data on the clinical efficacy of azithromycin as part of a treatment regimen for *Helicobacter pylori* eradication are available from randomised clinical trials published in the scientific literature, although there have also been contradictory results published, and *Helicobacter pylori* eradication rates varied considerably both for triple and quadruple therapy.

A meta-analysis by Dong et al. published 2009 evaluated 14 randomised trials that compared azithromycin-containing therapy with standard triple-therapy regimens for first-line treatment of *Helicobacter pylori* infection. Pooled *Helicobacter pylori* eradication rates were 72.01% (95% CI: 58.09%-85.93%) and 69.78% (95% CI: 66.47%-73.09%) for patients with or without azithromycin by intention-to-treat analysis. The authors concluded overall that azithromycin containing triple-therapy regimens could be equally effective in eradication of *Helicobacter pylori* compared with standard first-line triple-therapy regimens.

It is noted that the eradication rates in this meta-analysis were below the 80% referenced in the Points to consider on wording of Helicobacter Pylori eradication therapy in selected SPC sections (EMA 1999).

Other studies also do not show sufficient eradication rates of *Helicobacter pylori* with a treatment regimen that includes azithromycin as part of a combination therapy: Sullivan et al. 2002 investigated an azithromycin-based regimen with an already established clarithromycin-based regimen in the eradication of *Helicobacter pylori* infection in a prospective, randomised, blinded comparative analysis performed on 56 patients with upper GI symptoms and documented *Helicobacter pylori* infection. Patients were randomised to a treatment arm, which consisted of bismuth, clarithromycin, amoxicillin, and lansoprazole (B-LAC) or one consisting of bismuth, azithromycin, amoxicillin, and lansoprazole (B-LAA). To assess eradication, patients then received repeat endoscopy at 8 weeks from entrance into the study. Rapid urease test and histopathology were again used to evaluate infection. The results suggested that B-LAC was superior to B-LAA in the eradication of *Helicobacter pylori* and that the treatment regimen B-LAA containing azithromycin was not a suitable regimen in the treatment of *Helicobacter pylori* because of its substandard eradication rate.

Guideline recommendations

Spontaneous elimination of an *Helicobacter pylori* infection without prior eradication therapy is common in infants and young children, but rare from pre-school age and in adults. Therefore, all adult patients with evidence of active infection with *Helicobacter pylori* should be offered treatment. The treatment regimen for *Helicobacter pylori* eradication should overall consider local antibiotic resistance patterns, previous exposure and allergies to specific antibiotics (besides also cost, side effects, and ease of administration), meaning that the choice of initial antibiotic regimen should be guided by the presence of risk factors for macrolide resistance and the presence of a penicillin allergy. It is important to mention that eradication rate of conventional triple therapy (proton pump inhibitor (PPI), clarithromycin, amoxicillin or metronidazole) has declined progressively worldwide, particularly due to increasing clarithromycin resistance. Due to the resistance conditions and the resulting loss of efficacy, standard triple therapy has meanwhile become less important. According to the recent treatment guidelines, bismuth quadruple therapy (i.e. PPI, bismuth, tetracycline, metronidazole) is particularly recommended for empirical first-line therapy.

It is worth mentioning that according to current treatment guidelines, the aim of first-line treatment of patients with *Helicobacter pylori* infection should be an eradication rate of >90%. Although this goal is desirable, it is currently not realistic in view of the drugs available, the regulatory approval status and the poorer treatment adherence conditions frequently encountered in practice. However, treatment regimens that have achieved an eradication rate of at least ≥80% in intention-to-treat (ITT) analysis in randomised, controlled treatment trials should be used. To date, there is all in all insufficient data from RCTs to demonstrate ≥80% efficacy of azithromycin as part of a treatment regimen for HP eradication.

Azithromycin is not listed in European or international guidelines for the treatment of *Helicobacter pylori* infection.

Resistance development

None of the MAHs submitted data regarding the resistance rate of *Helicobacter pylori* to azithromycin; only clarithromycin-resistance data were provided for *Helicobacter pylori.* Azithromycin and clarithromycin are affected by the same resistance mechanisms, i.e. efflux pumps in the cytoplasmic membrane, change of target structure via methylation of the 23S rRNA or mutations in the 23S rRNA target structure/the large subunit ribosomal proteins and enzymatic inactivation of macrolides. It has been shown that mutations in the 23S rRNA confer cross-resistance towards clarithromycin and azithromycin in clinical *Helicobacter pylori* isolates. Additionally, because of their similar size (14- and 15-membered ring structure), clarithromycin and azithromycin are targeted by the same efflux pumps. Data on the transferability of clarithromycin-resistance via 23S rRNA methylation on azithromycin is scarce. Lastly, enzymatic inactivation of macrolides is of minor clinical relevance. Thus, based on the data discussed above, due to the cross-resistance to clarithromycin and azithromycin via 23S rRNA or mutations and efflux pumps and despite of some uncertainties, it is thought that general trends for azithromycin resistance in *Helicobacter pylori* can be derived based on clarithromycin data.

Bujanda et al. (2021) studied a time-trend analysis of *Helicobacter pylori* primary resistance to antibiotics in Europe collected from 2013 to December 2020. The average resistance rate to clarithromycin was 25% (95% CI, 16–34%), which was highest in 2016, with 34% of cases. A multicentre European study from 2018 reported elevated primary resistance of *Helicobacter pylori* towards clarithromycin (21.4%; range 4.8–36.9, 1211 patients included; Megraud et al., 2021), which is underpinned by national data from France (primary clarithromycin resistance 20% in 2022, secondary resistance was close to 50%) and Bulgaria (clarithromycin resistance rate of 30%, isolates collected between 2018 and 2022), but not reflected in the data of Sweden (resistance level of 1-10% in 2022).

2.2.12. Prevention of exacerbations of eosinophilic and non-eosinophilic asthma

The term "eosinophilic" asthma generally refers to the clinical inflammatory phenotype of asthma wherein a significant number of sputum, airway, and/or blood eosinophils are present. Conversely, individuals with "non-eosinophilic" asthma may still demonstrate low numbers of eosinophils, but the dominant inflammatory cell type may include neutrophils, mixed granulocyte inflammatory cells, or very few inflammatory cells, termed paucigranulocytic inflammation (Carr et al 2018). In asthma, exacerbations are periods where symptoms worsen. Exacerbations in both types can be clinically distinct, with eosinophilic exacerbations potentially causing more severe symptoms and requiring more intensive treatment (Heaney et al. 2021).

Clinical data

Azithromycin 500 mg three times a week for 48 weeks is authorised only in a few SmPCs (and none in products from the originator) as an additional drug for the prevention of exacerbations of eosinophilic and non-eosinophilic asthma in adult patients with symptomatic asthma, who are already receiving treatment with medium and high doses of inhaled glucocorticosteroids and a long-acting β-2 agonist. This is based on a randomised and double-blind study evaluating the above-mentioned dosing regimen (Gibson et al. 2017).

Various clinical trials have been performed, including with other regimens, to support the use of azithromycin for this indication with inconsistent results.

In a systematic review and meta-analysis of randomised controlled trials to assess the efficacy and safety of azithromycin in patients with persistent asthma, it was concluded that add-on therapy of azithromycin failed to improve asthma exacerbations and other relevant endpoints (Wang et al. 2019).

Similar conclusions were reached in another systematic review and meta-analysis that included seven randomised controlled trials, where azithromycin administration showed no significant improvement in FEV1, total airway inflammatory cells and symptom assessment (Tian et al. 2019).

2.2.13. Use of azithromycin for the treatment of malaria in the paediatric population

While treatment of malaria is currently not authorised with azithromycin in the EU, neither for adult patients not for the paediatric population, most of the azithromycin SmPCs included a section on azithromycin for treatment of uncomplicated malaria in children in section 5.1. This section is based upon a recommendation published in the European Public Assessment Report for paediatric studies in accordance with Article 46 of Regulation (EC) No 1901/2006 (Procedure Number: PT/W/0007/pdWS/001) published in 2019.

During the procedure, data from 4 clinical studies (A0661190, A0661157, A0661158, A0661201), as well as a literature articles (10 articles from 2000 to 2015) and malaria guidelines (UK malaria guideline from 2007; WHO malaria guideline from 2015) were assessed. The outcome of the assessment was, that non-inferiority of azithromycin monotherapy or combination therapy with chloroquine or artemisinin-based drugs in the treatment of uncomplicated malaria in children could not be demonstrated. These studies are considered a strong evidence against the use of azithromycin either as monotherapy or part of combine scheme for treating malaria.

During the Article 46 procedure, the SmPC Advisory Group and Paediatric Committee PDCO were consulted. The SmPC Advisory Group considered that, the results of all pharmacodynamics or efficacy studies conducted in children should be presented in Section 5.1, if the information is considered relevant to prescribers when managing paediatric patients with malaria or to prevent misuse. PDCO

agreed with the inclusion of the information in the SmPC in this specific case, based on the evidence / robustness of the data being analysed and considering the current and continued investigational activity in the field evaluating azithromycin used in malaria.

Inclusion of this data should be considered if the risk of off-label use would be reasonable. Although malaria treatment guidelines were updated in the meantime (WHO Guidelines for malaria (published 16th October 2023), still no recommendation for the use of azithromycin in this indication is included. All available guidelines and the standard of care do not recommend its use. In addition, consideration should be given to official guidance on the appropriate use of antibacterial agents, as recommended in section 4.1 of the azithromycin SmPC. A recent search of clinical trial databases did not show any on-going studies of azithromycin in malaria patients.

Altogether, the probability for off-label use of azithromycin (in combination with chloroquine or artemisinin-based therapies) in the malaria indication is currently considered to be low. Thus, the information on the non-inferiority of azithromycin alone or in combination for the treatment of malaria in paediatric patients with malaria should be removed from section 5.1 of the SmPC.

2.3. Pharmacokinetics

As part of the procedure, MAHs were asked to discuss of the adequacy of the recommended dosage and duration of treatment for the approved indications, 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 was requested from MAHs to justify the dosage and treatment duration in these populations. The below sections present the underlying data from MAHs to address these points.

2.3.1. Oral formulations

Absorption

The bioavailability of a single oral dose of 500 mg azithromycin is approximately 37% based on a comparison of AUC calculated up to 24, 48 or 72 h after dosing (Study 066-006; Foulds et al., 1990). The time to achieve C_{max} is 2-3 h.

Food effect

Several bioavailability studies in the fed and fasted state have been conducted with azithromycin showing that the effect of food on the bioavailability of azithromycin is formulation-dependent (study 066-057, Foulds et al., 1996).

As a consequence, the overall recommendation for the method of administration in section 4.2 of the harmonised SmPC is that all oral formulations (except the capsule formulation) of azithromycin can be taken with or without food, even though the administration immediately before a meal can improve their gastrointestinal tolerability. The capsule formulation should be taken either at least one hour before or two hours after a meal.

Distribution

Azithromycin is widely and rapidly distributed from plasma to the extravascular compartment, including tissues such as tonsil, lung and gynaecological tissues as well as the intracellular compartment (in particular to polymorphonuclear leukocytes, macrophages, and monocytes), from where it redistributes to plasma and extracellular compartment. Pharmacokinetic studies have shown considerably higher azithromycin concentrations in certain tissues (up to 50 times the maximum concentration observed in the plasma). This indicates an extensive binding with a steady-state volume of distribution ranging from 23 to 31 L/kg. The redistribution phase from the intracellular to the extracellular compartment and to the plasma may result in prolonged low concentrations after treatment cessation (study 066-057; Foulds et al., 1990 & 1993). This causes concern that azithromycin may promote the development of antimicrobial resistance as discussed in a number of published papers (Matzneller et al., 2013; Kong et al. 2019; Zheng et al. 2014). In addition, due to its extensive extravascular distribution, azithromycin is not recommended for the treatment of serious infections where high plasma concentrations may be needed. This is, for instance, the case of pneumococcal pneumonia that may course with associated bacteraemia. For that reason, a cross-reference has been added from the warning in section 4.4 related to antimicrobial resistance to section 5.2, where relevant information on this point has been included under the subheading Distribution.

Metabolism

Azithromycin is metabolised in the liver and excreted in the bile. Several metabolites were identified in bile with no significant antimicrobial activity. The primary route of biotransformation is N-demethylation of the desosamine sugar on the 9a position. Other pathways include O-demethylation, hydrolysis of cladinose (deconjugation of the cladinose sugar), and hydroxylation of desosamine sugar and macrolide ring (Peters, 1992; Schentag & Ballow, 1991).

There is no evidence of hepatic cytochrome P450 induction or inactivation via the formation of a cytochrome-metabolite complex. Also, auto-induced metabolism of azithromycin by this pathway has not been detected (Schentag & Ballow, 1991).

Elimination

The azithromycin elimination half-life in serum following an IV dose is consistent with that observed following oral administration of 500 mg daily with a 3-day regimen (about 66 h to 68 h; Amsden et al., 1999; Foulds et al., 1990) and closely reflects the tissue depletion half-life of 2.3 to 3.2 days (Foulds et al., 1990). Therefore, extensive uptake and subsequent release of drug from tissues may contribute to the long terminal half-life of azithromycin.

Urinary excretion is a minor elimination route and was approximately 12% and 5% within 72 h after an IV dose and an oral dose, respectively (study 066-006; Foulds et al., 1990).

Based on studies with immediate-release formulations, the majority of systemically available azithromycin is excreted unchanged in the bile (study 066-014).

Pharmacokinetics in special populations

Patients with renal impairment

In study AZM-NY-90-008 statistically significant differences in AUC_{0-120} (8.8 µg*h/mL vs. 11.7 µg*h/mL), C_{max} (1.0 µg/mL vs. 1.6 µg/mL), and CL_r (2.3 mL/min/kg vs. 0.2 mL/min/kg) following administration of 1 g azithromycin were observed between the group with GFR <10 mL/min (renal impairment) and GFR >80 mL/min (normal renal function).

The definition of renal function groups used in study AZM-NY-90-008 is however not in line with the current EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with

decreased renal function (EMA/CHMP/83874/2014). Thus, the GFR rate should be stated instead of the terms "mild/moderate" and "severe renal impairment" in the product information. Since azithromycin is mainly excreted by non-renal processes, the difference between renal function groups cannot be fully explained by differences in renal clearance. However, based on these results, no dose adjustment is necessary in patients with GFR 10–80 mL/min. In patients with GFR <10 mL/min azithromycin should be administered with caution.

Patients with hepatic impairment

The results of study AZM-I-90-001 demonstrate that the PK of azithromycin do not differ significantly between healthy volunteers and patients with mild or moderate hepatic impairment. Therefore, no modification of the azithromycin dosage is necessary for patients with mild to moderate hepatic impairment. However, PK has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and since azithromycin is primarily eliminated through the hepatobiliary route, azithromycin should be administered with caution in these patients.

Elderly

Based on the results of the PK study 066-212, it has been concluded that a dose modification is not considered necessary in the elderly – particularly since mean C_{max} (the relevant PK parameter for safety) was comparable in both age groups. However, according to the study report, azithromycin exposure was higher in elderly women compared to elderly man (AUC_{24}: mean increase up to 25%; C_{max}: mean increase up to 37.5%).

Due to the increased risk in the elderly of developing cardiac arrhythmia and torsades de pointes, a warning in section 4.4 of the SmPC was already included before the referral but was slightly modified during this procedure and in addition a cross-reference to section 4.4 was included in section 4.2.

Paediatric patients

PK data in paediatric patients are available from study 066-136 using oral suspension in children aged 6-15 years for treatment of streptococcal pharyngitis, study 066-172 in children aged 6 months to 5 years for otitis media and study 066-220 on safety and PK of a 3-day regimen (10 mg/kg daily) of oral azithromycin (oral suspension) in 16 patients 6 months to 10 years with bacterial infection.

Considering the study data, CHMP considered that the wording for section 5.2, subsection "Paediatric population" should present the PK parameters of study 066-136 and study 066-172 separately. The values of the PK parameters are approximately 1.7 times greater in children 6 to 15 years of age than in children 1 to 4 years of age. This does not seem to be the result of the underlying condition (pharyngitis versus otitis media) suggesting that there may be some relationship between azithromycin pharmacokinetics and age which justifies the recommendation included in section 4.2 of the SmPC of the powder for oral suspension regarding the recommendation to accurately measure the dose of 10 mg/kg (or 5 mg/kg for the 5-day regimen) for children weighing less than 16 kg (less than 3 years of age). Overlap of values however exists between the 2 groups.

2.3.2. Intravenous formulations

The information related to absorption, distribution, metabolism, elimination and PK in special populations is the same as for the oral formulations. No information on the paediatric population needs to be included as the IV formulations is currently only authorised for adult patients. Considering the available data, the following should be included in section 5.2 of the SmPC of the IV formulations:

"In patients hospitalised with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/ml, the mean

C_{max} ± S.D. achieved was 3.63 ± 1.60 µg/ml, the mean C_{trough} (C24) after the start of the final infusion dose was 0.2 µg/ml and the mean AUC0-24 was 9.6 ± 4.8 µg.h/ml.

The mean C_{max}, C_{trough} (C24) and AUC0-24 values were 1.14 ± 0.14 µg/ml, 0.18 ± 0.02 µg/ml, and 8.03 ±0.86 µg·hr/ml, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml.

Comparison of the plasma pharmacokinetic parameters following the first and fifth daily doses of 500 mg intravenous azithromycin in healthy volunteers showed almost no change in C_{max}, but there was a 40-61% increase in AUC0-24 reflecting a 2.2- to 3-fold increase in C_{trough} (C24) levels."

2.3.3. Drug-drug interactions

Considering a reasonable likelihood of co-administration with azithromycin, the following DDIs are supported based on the referred evidence from clinical studies PK data and/or post-marketing reports, and should be included:

1. In the text describing the interaction of azithromycin with medicinal products that are known to prolong the QT interval (beyond the medicinal products that were already uniformly included in the respective warning in section 4.4 of the SmPC that is moved to section 4.5 as a result of the current procedure):
    - Chloroquine and hydroxychloroquine, due to an increased risk of 30-day cardiovascular mortality, chest pain or angina and heart failure when co-administered (PSUSA/00000788/202304, Daby et al., 2021, Lane et al., 2020)
2. In the table listing active substances for which clinically relevant DDIs were observed:
    - Atorvastatin: increased risk for rhabdomyolysis (Strandell et al., 2009, Westphal et al., 2000.) after co-administration
    - Ciclosporin: increase in C_{max} and a narrow therapeutic index and more adverse reactions were reported upon co-administration in a MAH study.
    - Colchicine: increased serum levels in case of co-administration with azithromycin (PSUSA/00010491/201704, DiGiacinto et al., 2011)
    - Dabigatran – due to post-marketing data presented by Li et al. (2023) that found an increased risk for haemorrhages in patients receiving dabigatran concomitantly
    - Digoxin: *in vitro* and *in vivo* data from a study by Eberl et al. (2007) indicating increased digoxin exposure, and a population-based study by Gomes et al. (2009) indicating an increased risk for digoxin toxicity.
    - Warfarin: post-marketing reports indicating potentiation of anticoagulation upon co-administration and a retrospective cohort study by Penning-van Beest et al. (2008) indicating an increased bleeding risk upon co-administration of coumarins with azithromycin.

3. In the listing of medicinal products for which no clinically relevant change in the exposure of azithromycin or the other substance was observed upon co-administration based on clinical data:
    - Aluminium hydroxide and magnesium hydroxide (only for oral formulations)
    - Carbamazepine
    - Cetirizine
    - Cimetidine (only for oral formulations)
    - Efavirenz
    - Fluconazole
    - Methylprednisolone
    - Midazolam
    - Rifabutin

- Sildenafil
- Theophylline
- Triazolam
- Trimethoprim/sulfamethoxazole
- Zidovudine

The following DDIs should not be included in section 4.5 of the SmPC and section 2 of the PL:

1. As no products containing the respective active substance are currently marketed according to the Article 57 product database of EMA:
    - Astemizole
    - Didanosine
    - Indinavir
    - Nelfinavir
    - Terfenadine

2. As the data available does not provide sufficient evidence for inclusion of a DDI with azithromycin:
    - Ergotamine
    - other antibiotics
    - Alfentanil
    - Bilastine and mizolastine
    - Bromocriptin
    - Direct-acting oral anticoagulants:
        - Edoxaban
        - Other factor Xa inhibitors such as apixaban and rivaroxaban
        - Other thrombin inhibitors than dabigatran
    - Ivabradine
    - Phenytoin
    - Protease inhibitors other than indinavir and nelfinavir
    - Relugolix
    - Simvastatin
    - Sirolimus

2.4. Pharmacodynamics

Susceptibility

The efficacy of azithromycin depends mainly on the ratio between AUC (area under the curve) and MIC of the causative organism. Azithromycin covers a relatively broad spectrum of pathogens, including Gram-positive, Gram-negative, atypical and intracellular pathogens.

Due to low permeability of the outer membrane, most Gram-negative species are inherently resistant to macrolides, e.g. *Pseudomonas spp.* and Enterobacterales. However, in comparison to other macrolides, azithromycin shows a slightly better activity against Gram-negative bacteria.

Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive isolates. Macrolide-resistant isolates are found relatively frequently among Gram-positive facultative aerobic bacteria, in particular methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP). As discussed below, some ribosomal modifications determine cross-resistance

with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides (MLSB-resistance): the lincosamides (including clindamycin) and the streptogramin B.

Mechanisms of resistance

To date, various resistance mechanisms towards azithromycin are known, and are detected in isolates of clinically relevant bacterial species. The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are (1) target modification, (most commonly by methylation of 23S rRNA) and (2) efflux pumps (Wierzbowski et al., 2006). Enzymatic inactivation of macrolides, a third known resistance mechanism, is only of minor clinical interest. Cross-resistance between other macrolides (between azithromycin, clarithromycin, erythromycin and roxithromycin) has been reported.

No significant new information on azithromycin resistance mechanisms was found during the procedure. Covered resistance mechanisms range from efflux pumps in certain bacteria to mutations in ribosomal proteins, underlining the challenges in treating infections with evolving bacterial resistance.

Prevalence of resistance

Even if the data quality could be improved in some areas, diverse bacteria in distinct regions display varying degrees of resistance to azithromycin. Cumulatively, the data suggest an increasing global prevalence of azithromycin resistance among bacterial strains, with resistance developing against pathogens relevant to the approved indications of azithromycin in the EU/EEA. Detailed information about azithromycin resistance rates is included in the specific indication sections (see above in the Efficacy section).

Conclusion on pharmacodynamics

Based on the provided data, a harmonised wording is included in section 5.1 of the SmPC, including sections on mechanism of action, pharmacokinetic/pharmacodynamic relation, mechanisms of resistance, susceptibility testing interpretive criteria, and prevalence of acquired resistance.

2.5. Posology recommendations (dosing, duration and use in combination)

The authorised dosing regimens are mostly based on the clinical studies conducted during the clinical development of azithromycin that were performed in their majority more than 20 years ago, i.e. at a time when the epidemiological situation was different in terms of the prevalence of resistance in the organisms that are relevant for the approved indications. Additionally, the current availability of other measures such as pneumococcal vaccines and vaccines for the prevention of invasive disease due to *Haemophilus influenzae* are also responsible for the changing epidemiology for some infections.

While for certain infectious diseases, the use of extended regimens of azithromycin is recommended, for community-acquired pneumonia recent systematic reviews and meta-analysis for both paediatric and adult patients suggest that shorter courses of treatment may be equally effective as the standard 10-day regimen in (e.g.) adults.

Except for streptococcal tonsillitis and for erythema migrans (see above), no changes have been proposed by the CHMP in terms of doses and treatment duration due to the difficulties to support them with recent robust data. Of particular concern was the potential association between the use of single and high azithromycin dose for uncomplicated gonococcal and non-gonococcal urogenital disease and the emergence of macrolide-resistant *Mycoplasma genitalium* strains. For other indications minor adjustments and clarifications were introduced.

Due to the above uncertainties, a sentence is included in section 4.2, Posology of the SmPC stating that "*Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication*".

2.5.1. Oral formulations

Azithromycin oral formulations are marketed in the EU as granules/powder for oral suspension (e.g. 20 mg/ml and 40 mg/ml) or tablets/capsules of different strengths (e.g. 125 mg, 250 mg, 500 mg, 600 mg).

Two dosage regimens with a total dose of 1.5 mg azithromycin in adults and adolescents weighing at least 45 kg and 30 mg/kg azithromycin in paediatric patients aged 6 months and older are authorised for the treatment of infections of the upper and lower respiratory tract, acute bacterial otitis media, dental infections and skin and skin structure infections.

Following oral administration of a single 500 mg dose to 36 fasted healthy male subjects, the mean pharmacokinetic parameters were AUC_{0-72} = 4.3 µg*h/mL, C_{max} = 0.5 µg/mL, and T_{max} = 2.2 h (Study 066-042).

With a regimen of 500 mg on Day 1, followed by 250 mg daily on Days 2 to 5 (5-day regimen), PK parameters of azithromycin in plasma in healthy adults (18-40 years of age) were as follows: C_{max} was 0.41 µg/mL on day 1 and 0.24 µg/mL on day 5, while AUC_{0-72} was 2.6 µg*h/mL on day 1 and to 2.1 µg*h/mL on day 5. T_{max} increased from 2.5 h to 3.2 h (Study 066-212).

The 5-day regimen in adults consists of a single 500 mg dose on the first day, followed by a single 250 mg dose on days 2 to 5. Alternatively, a daily dose of 500 mg is given for three days (3-day regimen). For the paediatric population the 5-day regimen consists of a single dose of 10 mg/kg on day 1, followed by a single dose of 5 mg/kg on days 2-5. For the 3-day regimen, a single dose of 10 mg/kg is given for 3 days. The daily and total adult dose should not be exceeded in paediatric patients.

Pivotal studies for these indications have mainly been conducted with the 5-day regimen. However, cross-over studies in healthy adult volunteers comparing the PK of 1500 mg orally administered azithromycin when given as 3-day and 5-day regimen showed (apart from the slightly higher drug accumulation when administered as a 3-day regimen) no significant differences (Wildfeuer et al., 1993; Amsden et al., 1999). The terminal half-life in serum obtained by both regimens were about 66 h (Amsden et al., 1999) indicating that an effective concentration of azithromycin can be maintained for several days after administration.

More recently, concerns have been raised about the possibility that this prolonged half-life in tissues (extravascular) leads to low concentrations during the redistribution phase from the intracellular compartment once treatment is finished and that this promotes the development of resistance.

With respect to the paediatric population, the studies described in section 5.2 in paediatric patients show that even though there is some overlap in the systemic exposure between older and younger children, the latter (aged 1 to 4 years) may have less systemic exposure when treated at the same dose per kg of body weight. For that reason, for children weighing less than 16 kg, the SmPC and the PL indicate that the dose of azithromycin should be accurately measured, and these children should be dosed as closely as possible to the recommended dose, i.e., the formulation and the measuring device selected for these children should allow dose flexibility. As an example, the powder for oral suspension in sachets for which the minimum strength is 100 mg cannot be used to treat these children at the right dose. Therefore, the dosing tables and accompanying text for liquid oral formulations were updated to reflect the maximum daily dose per bodyweight and weight band for the individual mg/kg dosing regimens.

The subsection on method of administration for the oral formulations, in particular for powder for oral suspension in bottle has been rationalised.

Lower respiratory tract infections

The 3-day and 5-day regimen have been investigated in clinical studies and in most EU MSs either a 3-day regimen or a 3-day and 5-day regimen are currently authorised. Data of pivotal studies are supported by PK data. For example, in study 066-207 the tissue concentrations of azithromycin (after oral administration of 500 mg) was assessed in patients undergoing pulmonary resection. Pulmonary tissue concentrations of azithromycin were similar in samples taken at 24, 72 and 96 h post-dose (3.097, 2.550 and 3.940 µg/g, respectively) and were greater than the MICs of many common sensitive pathogens. Plasma levels of azithromycin were negligible at the same time points (0.134, <0.05, and <0.05 µg/mL, respectively). Moreover, Baldwin et al. (1990) showed that human bronchial samples, particularly alveolar macrophages (AM), contain very high levels of azithromycin after a single oral 500 mg dose, with mean peak levels 48 h post-dose of 2.18 µg/ml, 3.9 µg/mL and 23 µg/mL in ELF, bronchial mucosa and AM, respectively. When a 5-day regimen of oral azithromycin was given to healthy volunteers elevated drug concentrations in AM (>80 µg/ml) persisted up to 21 days and high concentration in ELF sustained for 7 days (with the highest mean concentration of 3.12 µg/ml after day 5) (Olsen et al., 1996). Recently, Hughes et al. (2020) developed an azithromycin population PK model using data from literature and individual clinical trials to predict concentrations in the lung, intracellular poly/mononuclear cells (PBM/PML), and AM. Predicted concentrations were higher in AM and PBM/PML, followed by lung tissue, and were lowest in serum. Simulated PBM/PML concentrations exceeded 4 µg/mL following the first dose and for ~ 14 days following 500 mg once daily for 3 days or 500 mg on 1 day/250 mg once daily on days 2–5. Simulated lung concentrations were above 1 µg/mL following the first dose and for ~ 10 days for both dosage regimens.

Based on the azithromycin concentration measured in pulmonary tissue, ELF and AM, treatment of lower respiratory tract infections including treatment of atypical pathogens seems to be reasonable and efficacy data for most entities are available. Moreover, efficacy of both regimens has been shown and since the 3-day and 5-day oral regimen can be considered comparable based on PK data, both regimens should be included in the product information provided that the product can be used for both regimens (e.g. the 500 mg tablet for treatment of adults and adolescents >45 kg has a score line and thus can be divided into equal doses for the 5-day regimen). Dosing recommendations in the paediatric population (based on body weight; max. total dose 30 mg/kg) are equivalent to the dosing recommendations in adults (total dose of 1500 mg) and as studied for other indications. Thus, authorised dosing recommendations are sufficiently justified.

Upper respiratory tract infections including sinusitis, pharyngitis, tonsillitis

The pivotal phase 3 studies have been conducted with the 5-day regimen and efficacy has been proven. However, due to the PK properties of azithromycin, a similar systemic exposure can be achieved with a 3-day regimen as already described above. In most EU MS either a 3-day regimen or a 3-day and 5-day regimen is authorised. Study 066-003 conducted in healthy subjects undergoing tonsillectomy showed that azithromycin distributed extensively into tonsillar tissue after two 250 mg doses (12 h apart) and was still detectable after 7.5 days (mean concentration 0.93 µg/g). The mean concentration of azithromycin in tissue 9-18 h after the second dose was more than 100-fold that in the serum (4.5 µg/g in tissue versus 0.03 µg/mL in serum). The tissue $t_{½}$ was 3.2 days (Foulds et al., 1991). In sinus fluid, a mean azithromycin of 0.65 µg/ml has been determined after a 500 mg dose (Margaritis et al., 2007).

Paediatric population

In clinical studies three dosing regimens based on body weight (12 mg/kg daily for 5 days, 10 mg/kg or 20 mg/kg for 3 days) were investigated for treatment of pharyngitis and two dosing regimens for treatment of tonsillitis (10 mg/kg or 20 mg/kg for 3 days). In the treatment of pharyngitis caused by *Streptococcus pyogenes* azithromycin has proved to be effective when it is administered at a dose of 10 mg/kg or 20 mg/kg for 3 days with a maximum daily dosage of 500 mg. At these two dosages a comparable clinical effect was observed, however, the eradication of the bacteria was more significant at a daily dosage of 20 mg/kg. Similarly, the dosing regimen of 10 mg/kg for 3 days was shown to achieve similar clinical response but inferior bacteriological eradication than the regimen of 12 mg/kg for 5 days. Thus, it has been agreed to include the following two dosing regimens in the product information: 20 mg/kg/day for 3 days and the 12 mg/kg/day for 5 days.

The dosing regimen of 10 mg/kg for 3 days has been removed from the posology section of the harmonised Product Information due to its inferior bacteriological eradication.

Efficacy of the 5-day regimen has been shown in adults and since the 3-day and 5-day oral regimen can be considered comparable based on PK data, both regimens should be included in the product information provided that the product can be used for both regimens (e.g. the 500 mg tablet for treatment of adults and adolescents >45 kg has a score line and thus can be divided into equal doses for the 5-day regimen).

Acute bacterial otitis media

Several clinical trials with different dosing regimens (3-day and 5-day regimen as well as single dose of 30 mg/kg) in the paediatric population have been conducted.

For treatment of adults in most EU MS either a 3-day regimen or a 3-day and 5-day regimen is currently authorised, while for treatment of children additionally the single-dose treatment is recommended in some EU MS. The single dose of 30 mg/kg is supported by PK data from healthy adult volunteers showing equivalent serum and white blood cell exposures whether a total dose of 1.5 g of azithromycin was given as a 1 day or 3-day regimen (e.g. serum $AUC_{0\text{-}inf}$ 13.1 µg*h/ml vs 11.2 µg*h/ml). However, as expected, the peak serum concentration (C_{max}) after a single dose was significantly higher than for the 3-day regimen (1.46 vs 0.54 µg/mL, respectively) (Amsden and Gray, 2001).

In a study of children with acute bacterial otitis media, azithromycin 10 mg/kg administered on day 1 followed by 5 mg/kg on days 2 to 5 (total dose 30 mg/kg) achieved mean peak middle-ear fluid concentrations of 8.6 and 9.4 µg/mL at 24 and 48 hours after the initial dose, respectively. In contrast, at 48 hours after treatment, azithromycin concentrations in plasma were ~300 times lower than those in middle-ear fluid (Pukander and Rautianen, 1996).

Three dosing regimens are approved for the treatment of paediatric patients with AOM, i.e. single dose of 30 mg/kg, 10 mg/kg/day for 3 days and 10 mg/kg on day 1, followed by 5 mg/kg/day on days 2-5.

All three dosing regimens in the paediatric population are supported by efficacy and PK data. The authorised dosing regimen (3-day and 5-day regimen) in adults is (except for the 1-day regimen) equivalent to the dosing recommendations in the paediatric population and acceptable.

Acute bacterial skin and skin structure infections

The pivotal phase 3 studies in adults have been conducted with the 5-day regimen for which efficacy has been proven. However, due to the PK properties of azithromycin, a similar systemic exposure can be achieved with a 3-day regimen as already described above. In most EU MS either a 3-day regimen or a 3-day and 5-day regimen is authorised.

The 5-day dosing regimen in adults is sufficiently justified by efficacy data. Since the 3-day and 5-day oral regimen can be considered comparable based on PK data, both regimens should be included in the product information provided that the product can be used for both regimens (e.g. the 500 mg tablet for treatment of adults and adolescents >45 kg has a score line and thus can be divided into equal doses for the 5-day regimen). Dosing recommendations in the paediatric population (based on body weight; maximum total dose 30 mg/kg) are equivalent with the dosing recommendations in adults (total dose of 1500 mg) and as studied for other indications. Thus, authorised dosing recommendations are sufficiently justified.

Erythema migrans

This indication is authorised in single MSs with the following dosing recommendation in adults (total dose of 3 g) and based on one RCT: 1000 mg on day 1, followed by 500 mg once daily on days 2-5.

For the paediatric population the following dosing regimen is authorised which is supported by studies by Arnez et al. (2002) and Arnez et al. (2015): 20 mg/kg on Day 1, followed by 10 mg/kg on Days 2-5 mg/kg.

The dosing regimen is supported by efficacy data. However, after review of more recent literature data on efficacy and current treatment guidelines, it has been suggested to prolong the treatment from 5 to 10 days in line with current EU and US treatment guidelines, as well as two studies that showed adequate efficacy in the 10 days regimen (see above under 2.2.5).

Dental infections

The pivotal Phase 3 study and most of the cited studies have been conducted with the 3-day regimen which are supported by PK data from Malizia et al. (1997). Azithromycin concentrations in plasma, saliva, and periodontal tissues were evaluated in 28 patients treated with the 3-regimen. The highest concentrations of azithromycin were observed 12 hours after the last dose in plasma, saliva, gingiva, and bone (0.33 mg/L, 2.14 mg/L, 6.47 mg/kg, and 1.86 mg/kg, respectively) and then declined gradually. However, consistent levels of the drug in saliva and periodontal tissues could be detected up to 6.5 days. Among the samples examined, the highest concentration of azithromycin was found in the gingiva at each time studied. Moreover, the ratios of salivary or periodontal tissue levels versus plasma concentrations remained nearly unmodified from 12 h up to 6.5 days.

The 3-dosing regimen is sufficiently justified by efficacy and PK data. Since the 3-day and 5-day oral regimen can be considered comparable based on PK data, both regimens should be included in the product information provided that the product can be used for both regimens (e.g. the 500 mg tablet for treatment of adults and adolescents >45 kg has a score line and thus can be divided into equal doses for the 5-day regimen). Dosing recommendations in the paediatric population (based on body weight; maximum total dose 30 mg/kg) are equivalent with the dosing recommendations in adults (total dose of 1500 mg) and as studied for other indications. Thus, the currently authorised dosing recommendations are sufficiently justified.

Sexually transmitted infections

The following dosing recommendations are currently authorised in EU MS:

- single 1000 mg dose for treatment of uncomplicated urogenital infections due to *Chlamydia trachomatis*

- single 1000 mg dose for treatment of chancroid/soft ulcer due to *Haemophilus ducreyi*

- single 1000 mg dose (in combination with 250 mg ceftriaxone) or 2000 mg single dose (in combination with 500 mg ceftriaxone) for treatment of uncomplicated urogenital infections due to azithromycin-susceptible *Neisseria gonorrhoeae*

- total dose of 4.5 g for treatment chronic prostatitis caused by *Chlamydia trachomatis* given as 500 mg daily for 3 consecutive days which should be repeated for 3 weeks

Efficacy of these regimens have been shown in clinical studies and are supported by the following PK data:

In study 066-208 the concentrations of azithromycin in gynaecological tissues after oral administration of a single 500 mg dose (2x 250 mg, capsule formulation) in patients undergoing gynaecological surgery was assessed. Azithromycin penetrated well into gynaecological tissue with a long residence time ($t_{½}$ about 67 hours). Mean azithromycin concentrations were between 1.44 µg/g (24 h post dose) and 0.78 µg/g (96 h post-dose) in gynaecological tissue. In a similar study (066-005) azithromycin were measured 14-19 h post-dose in fallopian tube (3.3 µg/ml), ovary (2.7 µg/ml), uterus (3.5 µg/ml) and cervix (2.8 µg/ml). Azithromycin concentrations in all tissue samples were more than 28-fold greater than those in serum.

Worm and Osterlind (1995) determined azithromycin concentrations in cervical mucus and plasma samples from 20 women with proven cervical chlamydial infection 1, 7 and 14 days after a single oral 1 g dose and found that in mucus azithromycin concentrations were above the MIC of *Chlamydia trachomatis*.

In study 066-001 the degree to which orally administered azithromycin (2x 250 mg, capsule formulation) distributes into prostatic and other urological tissues (testes, epididymis and kidney) has been assessed. Azithromycin distributed extensively in prostatic tissue and concentrations in prostatic tissue persisted long after drug in plasma declined to very low levels ($t_{½}$ of 73 h). The mean prostatic tissue concentration at 24-29.5 hours after the first dose was 2.2 µg/g while the mean concentration at 149 hours after the first dose was 0.62 µg/g.

The dosing regimens for oral azithromycin for the treatment of the above-mentioned sexually transmitted infections have been assessed in clinical studies performed in the 1990s. The epidemiological situation has changed that much since then however there is currently no recent data that would be able to challenge these dosing regimens. Particularly for diseases due to *Neisseria gonorrhoeae* (refer to data from the Euro-GASP surveillance project) azithromycin alone or in combination with ceftriaxone (the latter the mainstay of the treatment of gonococcal diseases) is no longer recommended in many treatment guidelines even though some of them have not been updated yet. In this respect, updates from the 2021 CDC Guidelines reported by Dalby and Stoner (2022) indicate that ceftriaxone monotherapy is recommended as the treatment of choice for gonorrhoea. Even though it is repeatedly alleged that azithromycin distributes to the sites of urogenital infection, this does not seem to be the only factor that influences azithromycin efficacy for this indication. Therefore, a specific warning is included in section 4.4 regarding sexually transmitted diseases in relation to the need for susceptibility testing prior to treatment of sexually transmitted infections, and the exclusion of certain pathogens before treatment of some of these infections.

Single dose azithromycin can still be considered an option for urogenital disease due to *Chlamydia trachomatis* and can continue to be reflected in the PI, but CHMP also noted that doxycycline, 100 mg twice per day for seven days is the preferred regimen by some European and American guidelines. As However, given the rapid changes in the treatment landscape of sexually transmitted diseases and the impact that treatment failures may have from a public health perspective, the posology tables in section 4.2 include a footnote prompting to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.

Pelvic inflammatory disease (PID)

See below under intravenous formulations.

Prophylaxis and treatment of disseminated MAC infections

For this indication, a 600 mg oral formulation is marketed in single EU Member States. The recommended dose is 1200 mg once per week for prophylaxis of disseminated MAC infections and 600 mg once daily for treatment of disseminated MAC infections based on clinical studies.

These dosing recommendations were supported by Study 066-062 and 066-077, which were Phase 1 PK studies to assess the azithromycin uptake by leukocytes and the absolute bioavailability of single oral doses of azithromycin following oral and IV administration of 1200 mg azithromycin or following oral administration of 250 mg or 600 mg doses daily for 22 days in HIV patients.

The efficacy of azithromycin for the prevention or treatment of MAC infections have not been established in children.

Prophylaxis of MAC infections in persons living with HIV with inadequate immune restoration and virologic control

A 1200 mg once weekly dose of azithromycin studied in two Phase 3 studies (066-155, 066-174) has been shown to provide effective prophylaxis of MAC infections. Moreover, it has been shown that high azithromycin concentrations are achieved with this dosing regimen in leukocytes and the slow release from these cells and the long elimination half-life of azithromycin allows a once weekly administration.

Thus, the dosage regimen of azithromycin 1200 mg once per week for prophylaxis against MAC infections in patients living with HIV is sufficiently justified. In case neither the 600 mg tablets nor the powder for oral solution are available to administer 1200 mg, it seems reasonable to use the 250 mg tablets to make a dose of 1250 mg instead of 1200 mg. This is supported by current treatment guidelines.

Treatment of DMAC infections in persons living with advanced HIV

Efficacy of the recommended dosing regimen of azithromycin 600 mg once a day has been shown in treating infections due to DMAC when administered in combination with other antimycobacterial agents that have shown *in vitro* activity against MAC such as ethambutol. PK data showed that sufficiently high azithromycin concentrations are achieved with this dosing regimen in white blood cells.

Thus, the dosing regimen of 600 mg azithromycin daily is sufficiently justified for oral formulations in adults and adolescents weighing at least 45 kg. As in the prior case, if the 600 mg strength is not available, the dose of 500 mg can be used. This is supported by current treatment guidelines.

The duration of therapy with azithromycin in the indication treatment and prophylaxis of MAC will depend on various patient-specific factors (e.g. ART, CD4 cell counts, safety and tolerability while on azithromycin therapy, other opportunistic infections), which must be taken into account by the treating physician. Given the above and the fact that SmPC section 4.2 include the following information: "Considerations should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication." length of azithromycin therapy is not included in SmPC section 4.2.

The two indications are proposed to be kept in section 4.1 for adults and adolescents weighing at least 45 kg for the solid and liquid formulations of azithromycin. In the case of the oral liquid formulations, this is restricted to subjects who are not able to swallow the solid formulations. In addition, currently these uses are expected to occur very rarely given current recommendations for treatment of HIV-1 and the availability of potent antiretroviral regimens.

Regarding children under 12 years of age, the safety and efficacy for the prevention or treatment of MAC have not been established. Based on paediatric pharmacokinetic data, it is said that a dose of 20 mg/kg would be similar to the adult dose of 1200 mg but with a higher C_{max}. Given that currently

the recommendation for children living with HIV is to initiate antiretroviral treatment as soon as the diagnosis is made and given the potential need for long-term treatment with azithromycin, an indication for prophylaxis or treatment of MAC infection continues to be not recommended for children.

2.5.2. Intravenous formulations

The intravenous formulation is authorised only for treatment of adult patients requiring initial IV therapy.

Community-acquired pneumonia (CAP)

Efficacy of azithromycin in treatment of CAP was shown in clinical studies. The authorised dosing regimen of the IV formulation is: 500 mg once daily for at least 2 days, followed by oral dose of 500 mg daily to complete a 7- to 10-day course.

In a multi-dose PK study healthy volunteers received 500 mg azithromycin intravenously over 3 h at a concentration of 1 mg/mL daily for five days. After the first dose, C_{max} averaged 1.08±0.13 µg/mL, while the C_{min} at 24 h averaged 0.06±0.01 µg/mL, and the AUC_{24} averaged 5.00±0.64 µg*h/mL. After the fifth dose, C_{max} increased by 6% (1.14±0.14 µg/mL) and AUC increased by 61% (8.03±0.86 µg/mL/h) (Garey & Amsden, 1999).

Safety and tolerability of the IV formulation was investigated in healthy volunteers for single doses up to 4000 mg infused over 2 h and for 500 mg dose once daily for up to five days (e.g. studies 006-234, 066-006 and 95CK33-0674).

In study 93CE33-0625A, the PK of azithromycin following multiple IV doses of 1 h infusions of 500 mg azithromycin QD for 2 to 5 days in hospitalised patients with CAP was investigated. Mean peak plasma levels of 3.6 µg/mL, mean AUC_{0-24} of 9.6 µg*h/mL, and mean trough level C_{24} of 0.20 µg/mL were determined. The mean azithromycin plasma concentration profile showed a rise up to C_{max} followed by a rapid fall in plasma levels within 1 h following the end of infusion.

With respect to the body weight distribution of adult patients enrolled in CAP studies of this formulation, in the PK study 93CE33-0625A, azithromycin C_{max} and AUC_{0-24} in female participants with body weight of 45 kg was 5.6 µg/mL and 19.6 µg*h/mL. While the MAH concluded that the systemic exposure to azithromycin is similar to that in participants with body weight above 50 kg, the CHMP noted that when these values are compared to those of the overall population of the study, it became evident that the systemic exposure is higher in the female subgroup, however overall no different dosage recommendations between male and female patients were considered necessary.

Given that late adolescents (aged 16 years) were only planned to be enrolled in a CAP study of IV azithromycin (study 066-138) which was terminated early due to poor enrolment, the indication of CAP for the intravenous formulation of azithromycin is restricted to adult patients (please refer to section 4). for a summary on agreed patient populations in the multiple dosage forms for CAP and AECB.

Pelvic inflammatory disease

The recommended dosing regimen is as follows, based on the efficacy and safety data of two pivotal trials: 500 mg once daily intravenous dose for at least 1 or2 days, followed by oral dose of 250 mg daily to complete a 7-day course.

This is supported by PK studies (066-208, 066-006) showing that azithromycin penetrates well into gynaecological tissue with a long half-life (see 2.2.8. above).

The dosing regimen for intravenous azithromycin was assessed in clinical studies and is supported by PK data. A switch to oral dose is foreseen in the SmPC of the intravenous formulation if clinically

indicated after 1 or 2 days of IV treatment, although this indication is currently not reflected in the SmPC of the oral formulations. Taking into account the bioavailability of the oral formulations, the CHMP was of the view that PID could be included in the product information of oral azithromycin formulations but restricted to adult women given the currently limited role of azithromycin for the treatment of PID and the scarce clinical data in the adolescent population.

Overall, the present role of azithromycin for the treatment of PID is limited given that it is only recommended as part of oral alternative regimens in very particular circumstances at the dose of 250 mg orally daily in combination with metronidazole 500 mg every 12 hours for 12–14 days. In the harmonised SmPC the recommendation is for a complete course of 7 days, with treatment to be initiated always intravenously. Monotherapy is seldom recommended and therefore the harmonised SmPC states that azithromycin should be used in combination with e.g. metronidazole.

2.6. Data on safety

Post-marketing data estimates that approximately 1350 million patients worldwide have been exposed to the originator´s azithromycin-containing medicinal products in the scope of this procedure since first approval. In contrast, regarding the cumulative post-marketing exposure to azithromycin of the MAH Teva (derived from the recent PSUR with DLP 30.04.2023), approximately n=547,186,381 and n=2,325,788 patients were treated with oral or parenteral formulations, respectively. This is considered a sufficiently large exposure to characterise the safety profile.

Main data sources in terms of post marketing safety data analysis were the latest available Core Safety Profile (CSP) for azithromycin from 2013, the currently valid Core Data Sheet (CDS) version 19.0 of the originator Pfizer (dated 10.08.2022), the Company Core Safety Information (CCSI) of the MAH Teva (dated 18.02.2022), SmPCs of different EU-MSs providing further safety related information beyond those included in the CSP and CDS, clinical efficacy studies mentioned above that also had safety objectives, and literature as well as scientific guidelines. Further data sources were the PSUSA ARs for azithromycin (systemic use) from 2014, 2017, 2020 and 2023, PRAC signal ARs for azithromycin, the originator´s currently approved Risk Management Plan (RMP) according to GVP Module V (Rev. 2) and the FDA´s United States Prescribing information (USPI).

Overall, the CHMP considers that these data sources provided sufficient information to widely confirm the established post marketing safety profile as included within relevant SmPC sections and the corresponding sections in the PL of most EU/EEA MSs. A summary of the information regarding the sections of the product information related to safety (on contraindications, warnings/precautions fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects and overdoses) is provided below:

Contraindications

Overall, as currently labelled in most MS only the following contraindication is supported based on the available data: "The use of azithromycin-containing products is contraindicated in patients with hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, or to any excipient listed in section 6.1.". The CHMP considered that no further data is available which indicate a need for additional contraindications.

Special warnings and precautions for use

This section was reviewed taking into consideration the already existing information in the different SmPCs, the available data from clinical studies and post-marketing and a consultation with the IDWP.

Besides the above-mentioned warnings related to AMR and on sexually transmitted infections, the CHMP identified based on the available data also the need to harmonise the warnings on severe skin

and hypersensitivity reactions, QT interval prolongation, hepatotoxicity, *Clostridioides difficile* associated diarrhoea (CDAD), pseudomembranous colitis, Myasthenia gravis, non-susceptible organisms, ergot derivatives and infantile hypertrophic pyloric stenosis (IHPS).

Safety related to drug-drug interactions and other interactions

See Pharmacokinetics section.

Fertility, pregnancy and lactation

This section was updated following consultation with PRAC (see below), to provide guidance based on the data in more than 7000 pregnancies and animal studies. Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Overall, CHMP agreed with PRAC to recommend that azithromycin should only be used during pregnancy if clinically needed.

Effects on ability to drive and use machines, undesirable effects and overdose

This section was harmonised to align with the available information from company core safety data from the originator companies.

Undesirable effects

Information provided within SmPC Section 4.8 ´Undesirable effects´ of nearly all MAHs appeared to be mostly consistent when compared with the EU CSP or originator CDS and CCSI, respectively. Most of the existing differences between some generic medicinal products and the respective reference medicinal products were minor and not substantial. These were addressed and reflected in the updated section 4.8. In this context, some terms have been adjusted to match the current MedDRA terminology/PTs (e.g. ”decreased appetite” has been substituted for ”anorexia” and ”Candida infection” for ”candidiasis”) and also some terms have been grouped (e.g. “loose stool” is considered to be sufficiently represented by the PT “diarrhoea” and has therefore been removed). The PL was updated accordingly.

Excipients of known effect

Azithromycin use in the paediatric population is extensive and therefore the fact that many of the authorised medicinal products, particularly the powder for oral suspension in bottle contain excipients considered as potentially harmful for the paediatric population is of concern. Two of these excipients are benzyl alcohol and ethanol that are included as ingredients of the flavouring agents of these formulations to mask the apparent bitter taste of the drug substance and improve its palatability. Within the EU, there are azithromycin-authorised products that do not contain these excipients. On the other hand, the content of these two excipients is variable for the same products authorised to the same MAH in different EU countries, thus discrepancies in exist in the product information. Azithromycin is included in the priority list of the WHO Paediatric drug optimization (PADO) group. Optimization of the available formulations is one of the areas of interest identified.

MAHS are reminded to keep their PI up to date in accordance with current guidance, including the QRD template and the excipients guideline.

2.7. Non-clinical aspects

No relevant new non-clinical data became available since the approval of azithromycin that would have an impact on the overall benefit-risk balance. However, some additional, supportive data with respect to embryotoxicity (Karbulut et al. 2008, Lu et al. 2023, Kemp et al. 2014) and proarrhythmogenic potential (Yang et al. 2017), were identified in the literature. These data do not change the overall

benefit-risk assessment or recommendations for use during pregnancy and lactation and were supporting a harmonisation of SmPC sections 4.6 and 5.3 and the PL accordingly, see also further details under 3. Expert Consultation below.

3. Expert consultation

The CHMP consulted the Infectious Diseases Working Party (IDWP) and the PRAC on several issues. Their respective advice is provided below.

1. PRAC advice to the CHMP

PRAC advice was sought regarding the use of azithromycin-containing medicinal products for systemic use in pregnancy.

The PRAC considered that there is a large amount of available data in pregnant women, which however does not support different level of risk between the trimesters of pregnancy. The PRAC also noted that data on the first trimester in view of miscarriage is inconclusive.

Considering the uncertainty of the data on the risk of malformations/abortions, the PRAC agreed to reflect this adequately in the product information and advised therefore that the following wording should be used in section 4.6 of the SmPC:

"There is a large amount of data from observational studies on exposure to azithromycin during pregnancy (more than 7000 azithromycin exposed pregnancies). Most of these studies do not suggest an increased risk of adverse foetal effects such as major congenital malformations or cardiovascular malformations.

Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Animal studies do not indicate reproductive toxicity (see section 5.3).

Azithromycin should only be used during pregnancy if clinically needed."

2. IDWP responses to the CHMP list of questions

As part of their responses to questions from CHMP, the IDWP recommended that the final agreed list of indications for azithromycin should not be restricted to situations in which other commonly used or recommended antibacterial agents cannot be used or are not considered appropriate. The WP considered the current sentence *"Consideration should be given to official guidance on the appropriate use of antibacterial agents."* sufficient to cover the variable rates of resistance observed across MS as well as different opinions and policies on which treatments should be considered first rather than second line, so that prescribers in various MS to consult national guidance as well as available relevant information on antimicrobial resistance in their country/region. There is also no mean percentage of resistance for a major pathogen that could justifiably be used to underpin removing an indication for use.

For **eradication of *Helicobacter pylori*** IDWP considered that to date the clinical demonstration in support of the use of macrolides in such an indication only relates to clarithromycin, which is the unique macrolide part of the therapeutic guidelines in this indication. The lack of robust clinical data in support of the use of azithromycin speaks against the use of this antibiotic in such indication.

For **treatment of acne vulgaris**, the IDWP considered that this indication can be removed from section 4.1 of the SmPC of azithromycin, considering that its long-term use for 9 to 12 weeks and beyond has been associated with macrolide resistance in C. acnes, a member of the normal skin microbiota and to disturbance of the latter. A call was made (Sardana et al. 2021) to restrict the use of oral azithromycin for acne which was based on the absence of regulatory approval in many EU MSs,

the risk of resistance, the indications of azithromycin for important infectious diseases and evidence showing that azithromycin is not superior to doxycycline or minocycline for acne. Consequently, the selection of non-antibiotic therapies is advocated.

Regarding **prophylaxis of *Mycobacterium avium* complex (MAC) infections,** based on the available data, the IDWP proposed some adjustment to the wording of the indication in section 4.1 to reflect it as "Prophylaxis of *Mycobacterium avium* complex (MAC) infections in people living with HIV with inadequate immune restoration." The IDWP noted that the need for prophylaxis would rarely occur, but in the few patients harbouring multi-resistant HIV strains with no optimal therapeutic management (e.g. those with CD4 counts < 50 cells/µL who remain viraemic on antiretroviral therapy), the need for MAC prophylaxis is still considered necessary.

Acute exacerbations of chronic bronchitis can be kept as an indication in section 4.1 of the SmPC in the view of the IDWP, considering that azithromycin is not considered a first option unless epidemiological data suggest the involvement of "atypical" organisms (Cantón et al. 2022) but its antibacterial spectrum of activity is the same as in the case of community-acquired pneumonia and, therefore, it can be also considered for the treatment of AECB.

On **odontostomatological infections**, IDWP recommended that this indication should be reworded as "Periodontal abscesses and periodontitis". Macrolides (including azithromycin) are not usually recommended due to increasing resistance among some strains of streptococci and their lack of optimal anaerobic activity. Its current use in clinical practice (which seems quite limited) is based on the lack of alternatives for penicillin-allergic patients, convenience (oral, once daily for 3 days) and PK/PD considerations, even though the clinical evidence supporting its use for this indication is very scarce. (Cantón et al. 2022, Peedikayil et al. 2016)

For **chronic prostatitis,** IDWP recommended that this indication can be kept in section 4.1 of the SmPC, provided that it is restricted to "Chronic prostatitis due to *Chlamydia trachomatis", considering that the general term covers a wide range of bacteria, while azithromycin* shows a good *in vitro* activity against *Chlamydia trachomatis*. It also distributes and concentrates in the prostatic tissue. Epidemiological data do not reveal high level of resistance of this pathogen against azithromycin.

IDWP also highlighted that chronic (bacterial) prostatitis is considered a complicated (urinary tract) infection. Therefore, it should be ensured that no wording implying that chronic prostatitis is an uncomplicated infection is part of the indication.

For **urethritis and cervicitis caused by *Mycoplasma genitalium***, IDWP noted that, this wording as such (i.e., urethritis and cervicitis due to *Mycoplasma genitalium*) is not included in section 4.1 of any of the SmPCs of azithromycin-containing medicinal products and it is not proposed by any of the MAHs, it can be considered part of a broad indication included in some SmPCs in the form of "mycoplasmosis".

In the current European guideline on the management of *Mycoplasma genitalium* infections (Jensen et al. 2022), azithromycin is included as first-line therapy for the treatment of uncomplicated *Mycoplasma genitalium* infection without macrolide resistance mutations or resistance testing. The regimen recommended is azithromycin 500 mg on day one, followed by 250 mg on days 2–5 (oral, total dose: 1.5 g). This regimen is also effective for the treatment of *Chlamydia trachomatis* uncomplicated infections. In contrast, azithromycin 1 g single dose (oral) is no longer recommended for the treatment of *Mycoplasma genitalium*, although it is effective for the treatment of *Chlamydia trachomatis*. Treatment of macrolide-susceptible *Mycoplasma genitalium* infections with a 1 g single dose of azithromycin results in selection of resistant-strain populations in 10%–12% of cases. Therefore, the regimen proposed for mycoplasmosis in the above mentioned SmPCs (single 1000 mg dose) carries a high risk of development of resistance. Similarly, treatment of uncomplicated disease due to *Chlamydia*

trachomatis with a single 1000 mg dose may lead to emergence of resistance in *M. genitalium* to azithromycin in those cases where the organisms is not identified, but present.

Therefore, the IDWP would suggest that an explicit indication for urethritis and cervicitis due to *M. genitalium* at the dosing regimen of azithromycin 500 mg on day one, followed by 250 mg on days 2–5 (oral, total dose: 1.5 g) is included in the SmPC of those azithromycin-containing medicinal products with appropriate pharmaceutical form and strengths. This same posology could be considered for *Chlamydia trachomatis*. A warning may be considered for section 4.4 of all SmPCs in relation to the risk that the single 1000 mg dose represents.

Regarding **pelvic inflammatory disease,** IDWP considered that this indication can be included in section 4.1 of the SmPCs of the oral formulations in the view of the IDWP provided that treatment has been initiated intravenously, however, *given the usual polymicrobial origin of the disease, combination therapy is always recommended (e.g. ceftriaxone ± metronidazole), also taking into account that resistance to azithromycin has increased in recent years. This is particularly the case if Neisseria gonorrhoeae is involved*.

The recommended posology is that treatment should always be initially commenced with IV azithromycin (if appropriate in the view of the treating physician), and then subsequently converted to oral therapy (in accordance with clinical response).

For prevention of **exacerbations of eosinophilic and non-eosinophilic asthma** the evidence available is not sufficient to support this indication in the view of IDWP, based on the following rationale: azithromycin 500 mg three times a week for 48 weeks is authorised in few SmPCs as an additional drug for the prevention of exacerbations of eosinophilic and non-eosinophilic asthma in adult patients with symptomatic asthma, who are already receiving treatment with medium and high doses of inhaled glucocorticosteroids and a long-acting β-2 agonist. This is based on a randomised and double-blind study (Gibson et al. 2017) described in section 5.1 of the concerned SmPC. In this study, the dosing regimen assessed is the same as above, but other regimens have also been assessed in other trials. Various clinical trials have been performed to support the use of azithromycin for this indication with inconsistent results.

In a systematic review and meta-analysis of randomised controlled trials to assess the efficacy and safety of azithromycin in patients with persistent asthma, it was concluded that add-on therapy of azithromycin failed to improve asthma exacerbations and other relevant endpoints (Wang et al. 2019).

Similar conclusions were reached in another systematic review and meta-analysis (Tian et al. 2019) that included seven randomised controlled trials, where azithromycin administration showed no significant improvement in FEV1, total airway inflammatory cells and symptom assessment.

Regarding the use of azithromycin for the **treatment of uncomplicated urethritis and cervicitis due to *Neisseria gonorrhoeae*** in view of the current prevalence of resistance, IDWP does not recommend restricting the indications for treatment of uncomplicated gonorrhoea.

However, the CHMP could consider a cross-reference from 4.1 to a statement in 4.4 that is similar to that placed in fluoroquinolone SmPCs to reflect near uniform resistance in MRSA. This could read as follows:

"Gonococcal cervicitis and urethritis and pelvic inflammatory disease

Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin (see section 5.1). Therefore, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin. If left untreated or treated sub-optimally, both conditions may lead to late onset complications such as infertility and ectopic pregnancy."

The IDWP also made wording proposals for all the indications.

In addition to the proposed actions with respect to sections 4.1 and 4.4, some members of the IDWP were of the view that the PK characteristics of azithromycin may be particularly of concern in what refers to the risk of emergence of resistance. Therefore, a recommendation was made to include a cautionary statement in section 4.4 of the SmPC, as follows: "In the decision-making process for the use of azithromycin, the risk of emergence of resistance in relation to its long half-life and extensive distribution to tissues and the safety profile of the drug, should be carefully weighed. Moreover, it should be considered that for several indications only targeted treatment is recommended (see section 4.1)."

Other members of the IDWP, however, strongly opposed to such statement. Considering that:

- Data has not been provided to support that azithromycin, based on its distribution to tissues and long terminal elimination half-life, has an increased risk of causing resistance compared with other macrolides or other antibacterials that lack these characteristics.
- There are no major concerns over the safety of this agent compared with other macrolides.
- The message of the last sentence of the proposal is unclear (*Moreover, it should be considered that for several indications only targeted treatment is recommended*).

4. Discussion and conclusions on benefit-risk balance

Available consumption data shows that the use of azithromycin has increased in recent years, including during the COVID-19 pandemic, whereas it is included in the WHO WATCH category, which carries the notion that "*These medicines should be prioritized as key targets of stewardship programs and monitoring*". At the same time, there is an increasing global prevalence of azithromycin resistance in several pathogens relevant to the approved indications.

In addition, there are significant differences between the product information of azithromycin-containing products across the EU/EEA, in particular in the approved indications and posology, but also in other sections of the product information. Several indications might be considered too broad 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).

Within this referral procedure, the CHMP critically reviewed all available data in relation to the efficacy and safety of the authorised indications for intravenous and oral azithromycin-containing medicinal products, including from clinical studies, pharmacokinetic and pharmacodynamic studies, epidemiological studies, susceptibility testing, scientific literature and post-marketing reporting information about resistance development against pathogens relevant for the approved indications in the EU, and a risk assessment on the probability of development of resistance during treatment as well as recommendations in current national and European treatment guidelines, considering that 1) azithromycin has been classified into the WATCH category by WHO, 2) data is suggesting an overuse of systemic azithromycin and 3) increasing resistance to azithromycin has been found in the EU. The CHMP also consulted the Infectious Disease Working Party (IDWP) and the Pharmacovigilance Risk Assessment Committee (PRAC).

In relation to a potential need to restrict the indications of azithromycin to second-line use, the IDWP pointed out that on the one hand the standard sentence in section 4.1 of the SmPCs "*Consideration should be given to official guidance on the appropriate use of antibacterial agents.*" sufficiently addresses the need to consult national or international treatment guidelines as well as available regional/national information on antimicrobial resistance by prescribers when choosing an antibacterial

agent. On the other hand, it was noted that this standard sentence has been included in the SmPCs of azithromycin-containing products for many years and that, despite this, consumption data suggest that azithromycin is prescribed too broadly and too often, and an increasing resistance of bacteria to azithromycin has been found in some MSs. Nevertheless, in view of the low level of safety concerns, and the fact that no threshold mean level of resistance above which a first-line indication would no longer be appropriate can be reasonably established, CHMP considered that the current data was not sufficient to support a restriction of indications to second-line. In order to maintain the use of azithromycin-containing medicinal products effective and safe in their therapeutic indications further outlined below it was considered more appropriate to include the following warning in section 4.4 of the SmPC: *"Potential for emergence of resistance: Azithromycin could favour the development of resistance due to the associated long-lasting and decreasing levels in plasma and tissues after the end of treatment (see section 5.2). Treatment with azithromycin should only be initiated after a careful assessment of the benefit and the risks, considering the local prevalence of resistance, and when preferred treatment regimens are not indicated."* This is supplemented by corresponding descriptions in section 5.2 of the SmPC, based on the existing data.

In addition, relevant for all indications, but particularly in the case of sexually transmitted diseases due to the rapid changes in the treatment landscape and the importance that treatment failures may have from a public health perspective, the following sentence has been included in section 4.2: *"Considerations should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication."*

Having reviewed all available data and taking into account current clinical guideline recommendations, the CHMP considered overall that azithromycin still remains an important therapeutic option in most therapeutic indications. The CHMP concluded that the benefit-risk balance of the azithromycin-containing medicinal products for systemic use are **positive** in the following therapeutic indications, however some of them required rewording as detailed below:

Lower respiratory tract infections (LRTIs)

The CHMP reviewed the data corresponding to this broad indication, with a view of refining it and specifying for which defined condition the benefit-risk balance of azithromycin is positive.

Community-acquired pneumonia (CAP)
While there is sufficient evidence supporting the efficacy of oral azithromycin in all populations, no clinical data are available for paediatric patients with CAP for the intravenous formulation. Therefore, the CHMP concluded that the benefit-risk balance is positive for azithromycin-containing medicinal products in the CAP indication for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, liquid oral formulations in paediatric patients aged 6 months and older weighing less than 45 kg and adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms, and intravenous formulations in adults.

Regarding atypical pneumonia, the CHMP agreed to the IDWP conclusions that the term CAP covers both atypical and typical organisms and thus atypical pneumonia does not need to be specified in the indications section of the SmPC.

Acute exacerbations of chronic bronchitis (AECB)
The CHMP agreed with IDWP that azithromycin is effective in treating AECB, however requested to restrict the indication AECB to adults only, where it is nearly in all cases diagnosed. Therefore, considering the available data on efficacy in the light of the known safety profile for azithromycin, the benefit-risk balance of azithromycin-containing medicinal products in the indication AECB is positive for solid oral formulations in adults weighing at least 45 kg, dispersible tablets in adults weighing at least

45 kg and liquid oral formulations in adults weighing at least 45 kg who are unable to swallow solid pharmaceutical forms.

Other LRTI

The indication "acute bronchitis" stated in Product Information (PI) at the start of this procedure is covered by the broad term LRTI, however, more recent reviews showed only limited evidence and small benefits in cough and activity level in patients with acute bronchitis. Current guidelines suggest that general antibiotics including azithromycin should not routinely be offered to adults or children with an acute bronchitis.

Regarding "exacerbation of bronchiectasis (AEB)" this was not explicitly stated in PI at the start, further, the European Guidelines for the management of adult lower respiratory tract infections (Woodhead et al. 2005) does not recommend macrolide antibiotics for the treatment of AEB. Instead, the European Respiratory Society guidelines for the management of adult bronchiectasis (Polverino et al., 2017) suggests long-term treatment with macrolides under certain circumstances which however is not covered by current approved dose regimens, and can lead to high levels of macrolide resistance.

Therefore, the CHMP, in line with the IDWP recommendation, considered that the wording of the indications under LRTIs should be restricted to AECB and CAP (including atypical pneumonia).

Upper respiratory tract infections (URTIs)

Under this broad indication, the CHMP reviewed the data relevant to streptococcal infections of the upper respiratory tract in studies on tonsillitis, pharyngitis and bacterial sinusitis, with a view of refining it and specifying for which defined condition the benefit-risk balance of azithromycin is positive.

Acute streptococcal tonsillitis and pharyngitis

The CHMP concluded that the benefit-risk balance remains positive for azithromycin-containing medicinal products in the treatment of acute streptococcal tonsillitis and pharyngitis, for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, liquid oral formulations in paediatric patients aged 6 months and older weighing less than 45 kg, and adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms. However, in the paediatric studies conducted, the dosing regimen of 10 mg/kg for 3 days was shown to achieve similar clinical response but inferior bacteriological eradication than the regimen of 12 mg/kg for 5 days. Therefore, the dosing regimen of 10 mg/kg for 3 days should be removed from section 4.2 of the SmPC, so the two dosing regimens which should remain for acute streptococcal pharyngotonsillitis are 20 mg/kg for 3 days or 12 mg/kg for 5 days.

Acute bacterial sinusitis

The CHMP concluded to a positive benefit-risk balance for azithromycin-containing medicinal products in the treatment of acute bacterial sinusitis for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, liquid oral formulations in paediatric patients aged 6 months and older weighing less than 45 kg and adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms.

Acute otitis media

Data from randomised clinical trials, microbiological data and literature data indicate that azithromycin is effective in the treatment of acute otitis media in children and is comparable to that of amoxicillin or amoxicillin/clavulanate.

Since AOM is uncommon in adults and the complications can be severe, it seems advisable to treat all adult AOM patients with antibiotics in addition to analgesic therapy. In the few published data available, amoxicillin or amoxicillin/clavulanic acid followed by cephalosporins are recommended as first-line therapies.

Current treatment guidelines are consistent in listing amoxicillin as the drug of first choice. The combination with clavulanic acid is only necessary in regions with increased β-lactamase formation of *Haemophilus influenzae* or *Moraxella catarrhalis*. In the current clinical guidelines, macrolides such as azithromycin are only considered for patients with penicillin allergies.

It should be noted that azithromycin is one of the more common antibiotics prescribed by paediatricians, particularly for respiratory infections and AOM, as azithromycin is easily administrable to children as an oral suspension, with once-a-day dosing for a relatively short treatment duration (three to five days) and a favourable side effect profile. However, the decision whether to use an antibiotic at all for the treatment of acute bacterial otitis media in children should be carefully considered. Due to the high spontaneous healing rate of AOM in the paediatric population of almost 80%, the benefit of an antibiotic needs to be assessed individually in relation to its risks, including the risk of the selection of more resistant bacteria on both an individual and collective level. The main problems with using azithromycin to treat acute otitis media, however, are recurrent resistant pneumococcal strains and a suboptimal clinical efficacy against *Haemophilus influenzae*, determined by bacterial eradication levels in middle-ear fluid (Ovetchkine et al., 2013). High and increasing resistance rates of over 30% have been described for infections caused by *Streptococcus pneumonia* isolates to macrolides including azithromycin, whereas the CHMP noted that the most common bacterial pathogens of AOM in children and adults is *Streptococcus pneumoniae*.

On balance as explained above, no additional restriction was considered warranted in section 4.1 of the SmPC, with the addition of the new warning on resistance in section 4.4. In view of the available data on efficacy in the light of the known safety profile for azithromycin, and following the IDWP advice, the CHMP concluded that the benefit-risk balance for azithromycin-containing medicinal products in the treatment of acute bacterial otitis media (AOM) remains positive for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, liquid oral formulations in paediatric patients aged 6 months and older weighing less than 45 kg and adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms.

However, the CHMP noted that prophylaxis/treatment of recurrent AOM, not previously specified as part of the indications, was not recommended in clinical guidelines. Considering the limited data the available in support the use of azithromycin for antibiotic prophylaxis/treatment of recurrent AOM, and following the wording suggested by IDWP for this indication, it was decided to leave this out of the AOM indication.

Acute bacterial skin and skin structure infections (ABSSSI)

In view of the available data on efficacy in the light of the known safety profile for azithromycin, the CHMP concluded that the benefit-risk balance of azithromycin-containing medicinal products in the indication ABSSSI is positive for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, liquid oral formulations in paediatric patients aged 6 months and older weighing less than 45 kg and adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms. In section 5.1, *S. aureus* is listed under the organisms for which acquired resistance may be a problem, however, as explained above, no additional restriction was considered warranted in section 4.1 of the SmPC, considering that a new warning on resistance was added in section 4.4.

Erythema migrans (early localised Lyme disease)
Considering the available data on efficacy in the light of the known safety profile for azithromycin, the CHMP concluded that the benefit-risk balance of azithromycin-containing medicinal products in the treatment of erythema migrans (early localised Lyme disease) remains positive for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, liquid oral formulations in paediatric patients aged 6 months and older weighing less than 45 kg and adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms. Further, as more recent studies and recent EU and US treatment guidelines recommend longer treatment duration with azithromycin in erythema migrans the CHMP considered that the treatment duration should be extended from 5 to 10 days in the dosing recommendations in section 4.2 of the SmPC.

Periodontal abscesses and periodontitis
The CHMP reviewed the data corresponding to the broad indication of dental / odontostomatological infections, with a view of refining it and specifying for which defined condition(s) the benefit-risk balance of azithromycin is positive. The indication "dental infections" was present in some SmPCs whereas "periodontal abscesses and periodontitis" was already included in other PIs. Most of the clinical trials where conducted in periodontal abscesses and periodontitis. Overall, within the field of dental infections CHMP, in line with IDWP, concluded that the azithromycin-containing medicinal products are efficacious in the indications "periodontal abscesses and periodontitis".

It has been, however, noted in guidelines that antibiotics should only be used as an adjunct to mechanical debridement and that good oral hygiene is crucial for long-term success, therefore physicians should consult the local official guidance as per the recommendation in section 4.1. In addition, the limited antibacterial activity of azithromycin against organisms of the *Bacteroides fragilis* group was highlighted leading to the inclusion of *Bacteroides* spp. in the list of organisms for which acquired resistance may be a problem in section 5.1 of the SmPC.

In view of the above, considering the available data on efficacy in the light of the known safety profile for azithromycin, the CHMP concluded that the benefit-risk balance of azithromycin-containing medicinal products is positive for the treatment of periodontal abscesses and periodontitis for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, liquid oral formulations in paediatric patients aged 6 months and older weighing less than 45 kg and adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms.

Sexually transmitted diseases caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae* or *Mycoplasma genitalium* (urethritis, cervicitis, chronic prostatitis)
The CHMP reviewed the data supporting the benefit-risk balance of azithromycin in the treatment of these conditions caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Consideration was also given to these when caused by *M. genitalium*, although it was not specifically referred to in pre-existing indications.

Clinical data showed that azithromycin is generally effective as a single oral 2 g dose for the treatment of acute gonococcal urethritis/cervicitis. However, the European Guideline on Diagnosis and Treatment of Gonorrhoea in Adults (2020) recommends that when azithromycin is used for gonococcal infections, it should be given in combination with ceftriaxone. The use of azithromycin in monotherapy for the treatment of urogenital infections due to *Neisseria gonorrhoeae* is not recommended unless the organism is shown to be susceptible. When immediate laboratory evaluations (e.g. Gram stain) of urethral specimens are accessible, the empiric treatment for gonococcal urethritis involves ceftriaxone.

As suggested by the IDWP, the CHMP considered that a warning should be added in section 4.4 to reflect the fact that *Neisseria gonorrhoeae* is very likely to be resistant to macrolides, including azithromycin. Therefore, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin. If left untreated or treated sub-optimally, this condition may lead to late onset complications such as infertility and ectopic pregnancy. The statement is cross-referred to at the beginning of section 4.1 and the warning itself cross-refers to section 5.1 of the SmPC where *Neisseria gonorrhoeae* is listed in the table listing the organisms for which acquired resistance may be a problem.

Regarding chlamydial urethritis/cervicitis, earlier studies and more recent literature data demonstrated that a single dose of azithromycin was as safe and effective as a standard 7-day regimen of doxycycline.

Regarding chronic prostatitis, azithromycin is known to show *in vitro* activity against *Chlamydia trachomatis*, therefore following the advice of IDWP this indication should be limited to this pathogen. The efficacy was also supported by the available clinical data.

While urethritis and cervicitis due to *Mycoplasma genitalium* was not mentioned in the indications, it can be considered part of a broad indication included in some SmPCs in the form of "mycoplasmosis". Based on the available EU treatment guidelines the IDWP suggested to include it explicitly in the authorised indication for those azithromycin-containing medicinal products with appropriate pharmaceutical form and strengths, with a 5-day treatment course. This was however not supported by CHMP considering the already high rates of selection for resistance mutations and more recent data indicating reduced efficacy (Mitjà et al. 2023). Furthermore, given that testing for *M. genitalium* may not be broadly available and due to the high risk of emergence of resistance in this organism, a warning was added to section 4.4 for concomitant urogenital infection by *Mycoplasma genitalium* to be excluded before considering the treatment of urethritis and cervicitis due to *Neisseria gonorrhoea* or *Chlamydia trachomatis* with the single dose regimens.

Considering the available data on efficacy in the light of the known safety profile for azithromycin, the CHMP concluded that the benefit-risk balance of azithromycin-containing medicinal products is positive for treatment of urethritis and cervicitis caused by *Chlamydia trachomatis or Neisseria gonorrhoeae* (the latter in combination with another appropriate antibacterial agent (e.g. ceftriaxone)), and chronic prostatitis caused by *Chlamydia trachomatis* for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, and liquid oral formulations in adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms.

Chancroid

Treatment of uncomplicated infections of the uro-genital tract by *Haemophilus ducreyi* with oral azithromycin is sufficiently supported the available data. The CHMP concluded that the benefit-risk balance of azithromycin-containing medicinal products is positive in the treatment of chancroid for solid oral formulations in adults and adolescents weighing at least 45 kg, dispersible tablets in adults and adolescents weighing at least 45 kg, and liquid oral formulations in adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms.

Pelvic inflammatory disease (PID), in combination with other appropriate antibacterial agent(s) (e.g. metronidazole)

Clinical studies showed similar efficacy of azithromycin alone or in combination in PID compared to other antibiotics, however, based on the current clinical guidelines, the role of azithromycin for the treatment of PID is limited given that it is only recommended as part of alternative regimens. In addition, monotherapy with azithromycin is seldom recommended and there is a general trend to add

metronidazole to all regimens for the treatment of PID. The PID indication is limited to adults only, considering that there is no relevant use of azithromycin for the treatment of pelvic inflammatory disease in children under 12 years of age and that the safety and efficacy in adolescent girls have not been established.

As explained above in relation to other sexually transmitted diseases, in view of the increased rates of resistance reported in *Neisseria gonorrhoeae* CHMP supported the suggestion from the IDWP to include a statement warning against empirical treatment with azithromycin and highlighting the need for susceptibility testing.

If azithromycin is used for the treatment of PID (which is only recommended as part of alternative regimens or in very concrete situations), treatment should always be initiated intravenously. While the SmPCs of the intravenous formulation foresee the possibility to switch to oral formulations to continue the treatment, PID was not reflected under 4.1 in those SmPCs. Therefore, and considering the supportive data available, the CHMP considered that the SmPC of the oral formulations should be aligned with the existing recommendations in the SmPC for IV formulations.

In view of the above, considering the available data on efficacy in the light of the known safety profile for azithromycin, the CHMP confirmed that the benefit-risk balance of azithromycin-containing medicinal products is positive in the treatment of PID in combination with other appropriate antibacterial agent(s) in adults for the intravenous formulation, and as follow-up treatment to IV azithromycin for the oral solid formulations, including dispersible tablets.

Disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection, in combination with ethambutol and prophylaxis of *Mycobacterium avium* complex (MAC) infection in people living with HIV with inadequate immune restoration

These indications are expected to occur very rarely given the current recommendations for treatment of HIV and the availability of potent antiretroviral regimens.

The test and treat approach with highly potent combined antiretroviral regimens have sharply reduced the likelihood of opportunistic infections thanks to the adequate and sustained immune restoration. Consequently, prophylaxis is no longer recommended if antiretroviral therapy has started according to EU treatment guidelines (EACS, 2023). Nevertheless, in the few patients harbouring multi-resistant strains with no optimal therapeutic management, the need for prophylaxis is still considered relevant in people living with HIV (PLWHIV) with CD4 counts <50 cells/µL who remain viraemic on antiretroviral therapy, this indication should therefore be limited to these patients.

Given the recommended posology of 1200 mg once weekly for MAC *prophylaxis*, this requires the availability of the 600 mg strength. However, as this strength is not generally available, the posology should be updated to 1250 mg once weekly (in line with EACS Guidelines version 12.0, October 2023) in the SmPCs including this indication but lacking the information on the appropriate strength.

With respect to *treatment* of disseminated MAC, clinical data found comparable efficacy of azithromycin and clarithromycin, and taking also into account on PK studies the CHMP agreed that a dose of 500mg or 600 mg once daily would be adequate. Adolescents weighing at least 45 kg are included in section 4.1 of the SmPC of the solid oral azithromycin formulations considering that efficacy can be extrapolated from adults with the same weight, while the efficacy of azithromycin for the prevention or treatment of MAC infections have not been established in children.

Current recommendations include the use of azithromycin at a dose of 500 or 600 mg once daily in combination with other antimycobacterial agents. Therefore, dosing recommendation should be aligned to the strengths available in the respective SmPC (i.e. revised to 500 mg or remain 600 mg once daily).

The duration of therapy with azithromycin in the indication treatment and prophylaxis of MAC will depend on various patient-specific factors (e.g. ART, CD4 cell counts, safety and tolerability while on azithromycin therapy, other opportunistic infections), which must be taken into account by the treating physician. Given the above and the fact that section 4.2 include the following information: "Considerations should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication." length of azithromycin therapy for these two indications is not included in section 4.2.

Furthermore, both indications were included in the SmPCs for liquid oral formulations in adults and adolescents weighing at least 45 kg, only when unable to swallow solid pharmaceutical forms.

Regarding children under 12 years of age, the safety and efficacy for the prevention or treatment of MAC have not been established. Based on paediatric pharmacokinetic data, a dose of 20 mg/kg would be similar to the adult dose of 1200 mg but with a higher C_{max}. Given that currently the recommendation for children living with HIV is to initiate antiretroviral treatment as soon as the diagnosis is made and given the potential need for long-term treatment with azithromycin, an indication for prophylaxis or treatment of MAC infection would not be considered appropriate for children.

In view of the above, considering the available data on efficacy in the light of the known safety profile for azithromycin, the CHMP concluded that the benefit-risk balance of azithromycin-containing medicinal products is positive for azithromycin in:

- Treatment of disseminated *Mycobacterium avium* complex (DMAC) infection in persons living with advanced HIV infection, in combination with ethambutol

- Prophylaxis of *Mycobacterium avium* complex (MAC) infections in persons living with HIV with inadequate immune restoration.

This applies to adults and adolescents weighing at least 45 kg for the 600 mg tablets (and 500 mg tablets, when it is already authorised), as well as for the dispersible tablets in adults and adolescents weighing at least 45 kg and for the liquid oral formulations in adults and adolescents weighing at least 45 kg who are unable to swallow solid pharmaceutical forms.

However, the benefit-risk balance of the following indications for the oral formulations of azithromycin was considered **negative**, and these should be removed from the product information of those products in which they are currently included:

- **Moderate acne vulgaris**
  Azithromycin was authorised in this indication in very few MS. However, over time the role of antibiotics in acne therapy has changed. Currently, oral antibiotics in general as part of a treatment regimen are considered a second- or third-line therapy in patients that did not respond to previous treatments. While there is data suggesting some efficacy for the treatment of moderate acne vulgaris with azithromycin, its use for 9 to 12 weeks and beyond has been associated to macrolide resistance in C. acnes, a member of the normal skin microbiota and to disturbance of the latter. The CHMP noted that according to current US guidelines referenced also by IDWP, azithromycin may have only a residual role for the treatment of moderate acne when tetracyclines such as doxycycline or minocycline are unsuitable. Sardana et al. 2021 recommended restricting the use of oral azithromycin for acne, considering the risk of resistance, the indications of azithromycin for important infectious diseases and evidence of low efficacy in acne therapy. According to the authors, consequently non-antibiotic therapies are advocated.

  Overall, considering the change in the therapeutic landscape towards non-antimicrobial treatments, the risk of long term treatment in terms of selection for resistance (supported by more recent

susceptibility data) together with the insufficient evidence available to support this indication, the CHMP, following the advice of IDWP, concluded that the benefit-risk balance of azithromycin-containing medicinal products in the treatment of moderate acne vulgaris is negative.

- **Eradication of *Helicobacter pylori***
  The management of *H.pylori* infections is well established in existing therapeutic guidelines and mainly relies more recently on a bismuth quadruple therapy (i.e. PPI, bismuth, tetracycline, metronidazole) for empirical first line therapy. Azithromycin is not listed in European or international guidelines for the treatment of *Helicobacter pylori* infection, this indication was authorised in two MSs. Treatment regimens that have achieved an eradication rate of at least ≥80% in intention-to-treat (ITT) analysis in randomised, controlled treatment trials should be used.

  To date, the clinical demonstration in support of the use of macrolides in such indication only relied on clarithromycin, which is the unique macrolide part of the therapeutic guidelines in this indication. Due to the design of study SUM-AD-05-97-HR-2, which included azithromycin treatment in both arms and thus did not compare azithromycin with an established standard treatment without azithromycin, this study is not considered sufficient to support the efficacy of azithromycin for *Helicobacter pylori* eradication. Even though data on clinical efficacy of azithromycin as part of a treatment regime for *Helicobacter pylori* eradication are available, a review of more recent scientific literature shows that the heterogeneity of combinations, doses and durations of treatment across the published studies (with eradication rates ranging from 15 to 90%) is such that an eradication rates of ≥80% of azithromycin as part of a treatment regimen for *Helicobacter pylori* eradication cannot be considered adequately demonstrated. All in all, no sufficient microbiological or clinical evidence from RCTs is available to support the efficacy of azithromycin in the indication 'Gastro-duodenal infections caused by *Helicobacter pylori* (*Helicobacter pylori*)'.

  In view of the above and considering the increasing resistance rate of clarithromycin in *Helicobacter pylori* and the high cross-resistance between macrolides, the CHMP, following the advice of the IDWP, considered the benefit-risk balance of azithromycin for the treatment of *Helicobacter pylori* infections negative.

- **Prevention of exacerbations of eosinophilic and non-eosinophilic asthma**
  Various clinical trials, including with other regimens, have been performed to support the use of azithromycin for this indication, with conflicting results. This indication was initially authorised in very few MS, based on a randomised and double-blind study evaluating this regimen as an add-on for the prevention of exacerbations of eosinophilic and non-eosinophilic asthma in adult patients with symptomatic asthma, who are already receiving treatment with medium and high doses of inhaled glucocorticosteroids and a long-acting β-2 agonist. However, two more recent systematic reviews and meta-analyses of randomised controlled trials concluded that add-on therapy of azithromycin failed to be effective to treat asthma exacerbations and other relevant endpoints.

  Therefore, the CHMP, following the advice of the IDWP, concluded that the benefit-risk balance of azithromycin for the prevention of exacerbations of eosinophilic and non-eosinophilic asthma is negative.

Other changes

The CHMP further considered that a number of additional changes were needed to the product information of azithromycin-containing medicinal products for systemic use.

In addition to the changes highlighted above, the posology and method of administration section was further revised to provide appropriate and up-to-date guidance on the use of azithromycin to

prescribers. The CHMP reviewed the current available data and harmonised the contraindications associated with the use of azithromycin.

The CHMP also reviewed the existing data on adverse reactions and exposure during pregnancy observed with the use of azithromycin and provided revisions for section 4.6 and 4.8 in accordance with the advice from PRAC.

Further changes considered necessary for the product information pertained to the updates of interactions, information on adverse events, and on the prevalence of resistance to azithromycin in the organisms that are relevant for the indications for which the benefit-risk balance is considered positive.

In addition, information recommending against the use of azithromycin for the treatment of malaria based on studies in children (PT/W/0007/pdWS/001) was removed from SmPC section 5.1. Considering that azithromycin is not recommended for treatment of malaria by any current treatment guideline and the low investigational activity evaluating azithromycin used in malaria, the CHMP concluded that the risk of off-label use was low. Therefore, the information on the negative study results is no longer relevant for prescribing physicians.

The package leaflet was amended accordingly.

MAHs are also reminded of their obligation to maintain the product information up to date, this includes the statements on excipients with known effect, as well as instructions for reconstitution and administration, particularly those of the powder for oral suspension in bottle.

Conclusion

Overall, the CHMP considered that the benefit-risk balance of azithromycin-containing medicinal products for systemic use remains favourable subject to the agreed amendments to the product information.

5. Grounds for Opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for azithromycin-containing medicinal products for systemic use.
- The CHMP considered the totality of the available data including from clinical studies, pharmacokinetics studies, pharmacodynamics studies, epidemiological studies, susceptibility testing, scientific literature and post-marketing reporting, submitted by the marketing authorisation holders in writing, as well as the outcome of a consultation with the Infectious Disease Working Party and the Pharmacovigilance Risk Assessment Committee (PRAC).
- The CHMP concluded that indications should be revised, but that the efficacy of azithromycin-containing medicinal products for systemic use continued to outweigh its risks, in different age groups depending on indications and with specificities in term of formulations in the treatment of:
    - Acute streptococcal tonsillitis and pharyngitis,
    - Acute bacterial sinusitis,
    - Acute bacterial otitis media,
    - Community-acquired pneumonia,

- Acute bacterial skin and skin structure infections,
- Erythema migrans (early localised Lyme disease),
- Periodontal abscesses and periodontitis,
- Urethritis and cervicitis caused by *Chlamydia trachomatis,*
- Urethritis and cervicitis caused by *Neisseria gonorrhoeae*, in combination with another appropriate antibacterial agent (e.g. ceftriaxone),
- Chronic prostatitis caused by *Chlamydia trachomatis,*
- Chancroid,
- Disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection, in combination with ethambutol,
- Acute exacerbations of chronic bronchitis,
- Pelvic inflammatory disease in combination with other appropriate antibacterial agent(s) (e.g. metronidazole),

and in the prophylaxis of *Mycobacterium avium* complex (MAC) infection in people living with HIV with inadequate immune restoration.

- In the context of evolving treatment standards and the concern over selection for resistance with long-term treatment, the CHMP considered that the data available do not demonstrate a positive benefit-risk balance of azithromycin-containing medicinal products for systemic use in the treatment of (moderate) acne vulgaris and of gastro-duodenal infections caused by *Helicobacter pylori*. Further, recent data cast serious doubts on the efficacy of azithromycin in the prevention of exacerbations of eosinophilic and non-eosinophilic asthma, and the CHMP concluded that the benefit-risk balance is also negative in this indication.
- The CHMP considered that new warnings should be included in relation to the potential for resistance in general, as well as the need for susceptibility testing prior to treatment of sexually transmitted infections, and the exclusion of certain pathogens before treatment of some of these infections. Special warnings and precautions were otherwise harmonised.
- The CHMP considered that revisions of the dosage regimen for azithromycin-containing medicinal products for systemic use were needed for streptococcal tonsillitis and erythema migrans, while adjustments were introduced for the various approved indications and patient subpopulations. In addition, the need to consider treatment guidelines was highlighted.
- The CHMP also reviewed the existing data on adverse reactions observed with the use of azithromycin-containing medicinal products for systemic use and concluded that the required updates to reflect the data adequately.
- Finally, the CHMP recommended updates to the adverse events section and to the recommendations for pregnancy and lactation in the product to reflect the available clinical and non-clinical data on exposure in pregnancy. The interactions as well as pharmacokinetic and pharmacodynamic data in the product information also needed to be updated.

In view of the above, the Committee considers that the benefit-risk balance of azithromycin-containing medicinal products for systemic use remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for azithromycin-containing medicinal products for systemic use.

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German national guidelines:

S3-Leitlinie Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie

https://register.awmf.org/de/leitlinien/detail/020-020

S3-Leitlinie Odontogene Infektionen

https://register.awmf.org/de/leitlinien/detail/007-006

Aktualisierte S2k-Leitlinie Helicobacter pylori und gastroduodenale Ulkuskrankheit

https://register.awmf.org/de/leitlinien/detail/021-001

NICE Guidelines:

Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing.

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