Annex II

Scientific conclusions

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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).

Overall summary of the scientific evaluation

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 *H. 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 *C. trachomatis*, *N. gonorrhoea* or *M. 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 *C. trachomatis* and *N. gonorrhoea*. 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 *M. 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 *N. gonorrhoeae* or *C. 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 *H. 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 *H. pylori* eradication. Even though data on clinical efficacy of azithromycin as part of a treatment regime for *H. 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 *H. 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* (*H. pylori*)'.

In view of the above and considering the increasing resistance rate of clarithromycin in *H. 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 *H. 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.

Grounds for CHMP 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.

CHMP opinion

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