EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 May 2022
EMA/CHMP/187859/2017
Committee for Medicinal Products for Human Use (CHMP)

Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements

Draft agreed by Infectious Disease Working Party (IDWP)	February 2018
Adopted by CHMP	22 March 2018
Start of public consultation	06 April 2018
End of consultation (deadline for comments)	30 October 2018
Agreed by IDWP	July 2021
Adopted by PDCO	22 April 2022
Adopted by CHMP	19 May 2022
Date of coming into effect	1 December 2022

This addendum complements the Guideline on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 3).

Keywords	***Antibacterial agent, paediatric population, extrapolation, study designs, timing paediatric studies***

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Executive summary

This addendum to the *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 rev 3) has been developed to provide guidance on clinical development programmes that are required to support the authorisation of antibacterial agents for treatment of infectious diseases in paediatric patients.

For antibacterial agents with suitable spectra of activity, an extrapolation of efficacy from adults and/or from an alternative source population (i.e. from any one or more of adults, adolescents or children above a certain age) to a target paediatric population below a certain age is possible based on similar pathophysiology of the infectious disease across the target age groups. This situation applies to the majority of infectious diseases that occur in all or in a wide range of age subgroups. An extrapolation concept needs to be developed and detailed in an extrapolation plan.

There are some infectious diseases for which it is considered necessary to generate efficacy data in certain paediatric age subgroups. For example, when an infectious disease occurs only or very predominantly in children below a certain age. Guidance on trials that may be conducted in these exceptional cases is provided in this Addendum.

For antibacterial agents, an extrapolation of efficacy between age subgroups (most often from adults ± adolescents to children aged from birth to less than 12 years) usually relies primarily on matching the systemic exposures (i.e. AUC and Cmax) when using the dosing regimens selected for each of the relevant paediatric age subgroups to those in adults or other source population(s) in which efficacy has been demonstrated based on population pharmacokinetic (POPPK) analyses. To avoid undue delay in reaching conclusions on potentially suitable dose regimens, the initiation of paediatric pharmacokinetic (PK) studies should be considered in relation to the expected time of availability of safety and efficacy data in adults or other source population(s).

Additional support for the selected paediatric dose regimens should be provided by pharmacokinetic-pharmacodynamic (PK-PD) modelling and simulation, with estimation of the probability of target attainment (PTA). The results of PK-PD analyses are particularly important if there are mismatches in PK parameters between age subgroups.

The safety profile in all age groups will be driven mainly by systemic exposure to the antibacterial agent. For the most part, a similar safety profile is expected across age sub-groups whenever paediatric dose regimens achieve similar systemic exposures to those in other age sub-groups.

On occasion, safety data may need to be generated in the paediatric population or in specific age subgroups if concerns arise from the available non-clinical and/or clinical data that are especially relevant to children (e.g. age-specific adverse effects such as those of fluoroquinolones). In these instances, the need to adequately document safety in children has implications for the size of the pre-approval paediatric safety database. Depending on the amount of data generated in the paediatric population, mitigation measures to deal with uncertainty and risk should be proposed. For example, post-marketing measures to collect additional safety data in the paediatric population.

1. Introduction (background)

The *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 rev 3) provides guidance that is mainly focussed on adult clinical development programmes. This Addendum to the above mentioned guideline considers the various situations that could apply and the paediatric data that should be generated for approval of antibacterial agents in the paediatric population, including whether pharmacokinetic data may suffice to allow the extrapolation of

indications for use of an antibacterial agent in adults and/or other source population(s) to all or specific subgroups of children.

2. Scope

This Addendum provides guidance on clinical data requirements to support the approval of an antibacterial agent to treat infectious diseases in paediatric patients when:

- Extrapolation of efficacy against an infectious disease across age subgroups is possible based on similar pathophysiology and aetiology. This situation applies to the majority of infectious diseases.
- Extrapolation of efficacy against an infectious disease from adults and/or other source population(s) to paediatric patients is not possible because the infectious disease occurs only or predominantly in a specific subgroup of paediatric patients (e.g. impetigo and acute otitis media occur predominantly in children aged < 5 years) and/or there are differences between age groups in the nature or course of the infectious disease that may lead to different responses to treatment (e.g. streptococcal pharyngitis).

The considerations for extrapolation of safety across age subgroups are addressed, taking into account any age-related safety concerns from the available non-clinical and/or clinical data.

This Addendum considers antibacterial agents that are administered by parenteral, oral or topical routes (i.e. direct application to skin, mucous membranes or conjunctivae). It does not address the clinical development of inhaled antibacterial agents (e.g. those intended for treatment of lung infections in children with cystic fibrosis).

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, as well as Regulation (EC) No 1901/2006, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- ICH E11 and ICH E11 addendum R1: Guideline on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99);
- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005);
- Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2);
- ICH guideline S11 on nonclinical safety testing in support of development of paediatric pharmaceuticals;
- Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008);
- Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 3);
- Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/456046/2015);
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum);

- Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018).

4. Patient selection

Pharmacology studies

4.1. Pharmacokinetic studies

Paediatric pharmacokinetic studies with antibacterial agents are usually performed in children with suspected or confirmed bacterial infections (see also section 6.1). In these cases, age-appropriate diagnostic criteria for specific infectious diseases (such as those developed and published by professional bodies) should be used for paediatric patient selection.

The paediatric pharmacokinetic data may be obtained in patients with one or a limited range of the infectious diseases for which use of the antibacterial agent is proposed, taking into account whether available data indicate that pharmacokinetics may differ depending on the site of the infection. It is recommended that pharmacokinetic data are obtained from at least some paediatric patients with evidence of severe systemic illness, if applicable to the indications proposed.

In term and preterm neonates, it may be difficult or impossible to determine the primary site of infection and it may be necessary to obtain pharmacokinetic data for the test antibacterial agent in patients with an unknown primary focus who are receiving standard of care antibacterial regimens.

4.2. Efficacy studies

In the very few situations outlined in sections 5.2 and 6.2 in which a demonstration of efficacy may or would be required in a paediatric population, available age-appropriate diagnostic criteria for specific infectious diseases (such as those developed and published by professional bodies) should be used for patient selection.

5. Assessment of efficacy

5.1. Infectious diseases for which an extrapolation of efficacy between age subgroups is possible

Whenever efficacy data are available in adults and/or other source population(s), an extrapolation of efficacy to paediatric patients should be attempted. See further in section 6.

The application dossier should include a discussion of the basis for the extrapolation of efficacy from a pre-defined source population to various paediatric age subgroups, including justification for the sufficiency of the paediatric pharmacokinetic data to support the proposed dose regimens.

An extrapolation of efficacy across age subgroups is considered possible for the majority of infectious diseases including, but not limited to, the following:

- Acute bacterial skin and skin structure infection (ABSSSI)
- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI)
- Uncomplicated urinary tract infection (uUTI)

- Community-acquired pneumonia (CAP)
- Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)
- Pelvic inflammatory disease
- Sexually transmitted diseases (when acquired through the sexual route)
- Acute bacterial sinusitis
- Acute bacterial endocarditis. Efficacy is most likely to have been demonstrated in adults with right sided endocarditis and without prostheses whereas infective endocarditis in paediatric patients may also be due to a left sided or septal focus. Nevertheless, the causative pathogens and duration of treatment is similar and an extrapolation between age groups is possible.
- Acute bone and joint infections, exception for acute haematogenous osteomyelitis.
- Travellers' diarrhoea and *Clostridioides difficile* infection
- Acute bacterial conjunctivitis (for topical formulations of antibacterial agents)

For agents administered topically to skin and mucous membranes, an extrapolation is considered possible for superficial wound infections and for those secondarily infected dermatoses that are more common in adults than in children (e.g. infected psoriasis).

Similarly, it is considered that an extrapolation of efficacy across age groups is possible for antibacterial agents that are indicated for the treatment of infections due to certain bacterial species in patients with limited treatment options. To support this type of extrapolation, it is not required that PK data are obtained specifically from children infected with multi-drug resistant organisms that are the target of the antibacterial agent.

5.2. Infectious diseases for which an extrapolation of efficacy between age subgroups is not possible

A demonstration of efficacy in the target paediatric population to support an indication for use in a specific age range is usually required when:

i) An infectious disease occurs only or mainly in the paediatric population so that efficacy trials in older patients, such as adults, are either not feasible or cannot be considered sufficient for approval of the paediatric indication (e.g. impetigo, infected atopic dermatitis, acute otitis media);

ii) Any of the bacterial aetiology, course of the disease and/or response to treatment may be different between age subgroups (e.g. acute Group A streptococcal pharyngo-tonsillitis, acute haematogenous osteomyelitis).

See further in section 6.2.

5.2.1. Studies confined to the age group(s) in which the infectious disease is most prevalent

An extrapolation of efficacy against a specific infectious disease from a study conducted in the age group most commonly affected to other age groups could be considered on a case by case basis and subject to adequate justification of dose regimens.

5.2.2. Studies enrolling all age groups which may be affected by the infectious disease

If a single efficacy study enrolling various age groups is planned, the study population should include a representative sample that belongs to the paediatric age subgroup(s) in which the disease most commonly occurs. A formal (i.e. statistically powered) demonstration of efficacy in pre-defined age subgroups is not required but results should be presented by, and should be generally consistent across, the age strata.

6. Study design

6.1. Pharmacokinetic studies

Applicants should refer to the *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population* (EMEA/CHMP/EWP/147013/2004 Corrigendum). The timing of paediatric pharmacokinetic studies needs to be carefully considered in relation to the source population (most commonly adult) data that are available, particularly when the test antibacterial agent is intended to be administered to paediatric patients as a full course of treatment for their infectious disease. The amount of pharmacokinetic data collected from paediatric patients should suffice to support dose selection as described below in section 6.1.1. Consideration should be given to enrol adolescent patients in phase 3 adult studies.

As stated in section 4.1, it is usual that pharmacokinetic data for antibacterial agents are obtained from paediatric patients who have an underlying infectious disease. Depending on the known pharmacokinetic properties of the test antibacterial agent:

- If single dose pharmacokinetic data are considered adequate to select paediatric dose regimens it is recommended that the test antibacterial agent is administered to paediatric patients who are also receiving routine antibacterial therapy for their infectious disease.
- If multiple dose pharmacokinetic data are required to adequately assess plasma exposures, it is usual that paediatric patients receive a full course of the test antibacterial agent for treatment of their infectious disease, either alone or as adjunctive therapy. If this approach is not considered appropriate, a sufficient number of doses should be administered to provide adequate PK data to support modelling and simulation.

When the test antibacterial agent is administered with other antibacterial agents, there should be prior knowledge of the potential for drug-drug interactions to occur.

Unless there are suspected or identified safety concerns that are known or likely to be exposure-related, pharmacokinetic studies in paediatric age subgroups may be conducted in parallel except for antibacterial agents for which age and maturation-related differences in drug disposition are expected, in which case a staged approach to enrolling specific paediatric sub-groups should be employed. However, it may not always be necessary to obtain pharmacokinetic data from all age subgroups in which use is to be proposed. For example, for some test antibacterial agents that have very simple pharmacokinetics, modelling and simulation using adult data pharmacokinetic data may be sufficient to support dosing recommendations for other age subgroups (see section 6.1.1 below). Nevertheless, unless the test agent is unsuitable for children aged < 2 years, pharmacokinetic data should be generated in the age range from birth to 2 years of age owing to the rapid developmental changes during the first two years of life that can impact on any of absorption, distribution, metabolism and excretion of pharmacologically active agents. On the other hand, owing to the lack of significant

developmental changes affecting pharmacokinetics, adolescent patients could be enrolled in adult trials.

6.1.1. Systemic administration to achieve a systemic effect

This section considers situations in which it is necessary to generate paediatric pharmacokinetic data to support an extrapolation of safety and efficacy from the source population to the paediatric population, using modelling and simulation to identify appropriate paediatric dose regimens.

When bridging safety and efficacy from the source population(s) to the target paediatric population(s), the Cmax and AUC are the primary pharmacokinetic parameters for comparing exposures. The paediatric dose regimen(s) should also provide adequate probability of target attainment (PTA) to support bridging efficacy between populations. The following issues should be considered in this regard:

Firstly, for some antibacterial agents it may be very difficult to identify paediatric dose regimens that provide closely matched plasma pharmacokinetic profiles (e.g. this may occur if the rate of excretion is very different across age subgroups, with or without different magnitudes of inter-individual variability). In these situations, pharmacokinetic-pharmacodynamic (PK-PD) analyses and probability of target attainment (PTA) estimations based on simulating a range of regimens may serve to select the regimen(s) that are most likely to provide similar efficacy in paediatric patients compared to the source population.

Secondly, it is expected that a paediatric dose regimen that achieves a similar AUC to that in adults will commonly be associated with a relatively lower Cmin. This may lead to lower PTA with paediatric dose regimens if the PK-PD index for the test antibacterial agent is the percentage of time the unbound drug concentration in plasma exceeds the minimum inhibitory concentration (%*f*T>MIC). In such a case, measures to maintain at least a comparable AUC but increase the PTA in children could include:

- increasing the dose (subject to safety considerations) and/or
- decreasing the dosing interval (i.e. increasing dose fractionation over 24 hours) and/or
- increasing the duration of the infusion, noting that long infusion times may be problematic in some paediatric age groups.

The potential effects of these measures to improve the PTA should be assessed as needed in modelling and simulation exercises. If considered necessary, paediatric regimens selected in this way could be used in pharmacokinetic studies in appropriate age subgroups.

6.1.2. Topical or oral administration to achieve a local effect

In these cases, dose regimens for paediatric patients cannot be identified based on comparable plasma exposures to those in the source population(s) in which safety and efficacy were demonstrated.

For topical agents, provided that the pharmacokinetic and physicochemical properties of the antibacterial agent and its formulation do not suggest that substantially higher systemic exposures of potential concern are at all likely to occur in paediatric patients, and subject to the nonclinical data, it may be appropriate to administer the same product (i.e. formulation and strength) to all age groups and to document that there is negligible systemic exposure to support the extrapolation of safety. There is particular concern regarding systemic exposures that may result from topical treatments in children below 2 years of age due to the uncertainties about the age at which the skin barrier function can be considered fully mature and the age-dependent larger ratio of body surface area to body weight, which may predispose to increased systemic absorption compared to older subjects.

For oral agents, it may be appropriate to administer the adult dose in an age de-escalating fashion unless or until there is evidence of local intolerance below which a reduced dose could be needed. If necessary, the selection of a reduced dose for some paediatric age subgroups could be based on factors such as drug solubility measurements in simulated intestinal fluids, estimated age-related gut volumes and physiologically-based pharmacokinetic models. Negligible systemic exposure when administering the selected doses should be documented to support the extrapolation of safety between age subgroups.

6.2. Efficacy studies

Efficacy studies in the paediatric population will be needed in very few situations (see section 5.2).Some examples include, but are not limited to, the following:

Impetigo

This occurs predominantly in paediatric patients aged less than 5 years. The same pathogens cause impetigo across age groups but the spontaneous resolution rate at a fixed time point after commencing treatment may vary by age. Therefore, either the efficacy trials should be conducted in children aged less than 5 years to support paediatric use or the trial populations should include an adequate representation of children in this age group.

Placebo-controlled studies should be performed in patients with impetigo because the high spontaneous resolution rate makes an approval based solely on non-inferiority studies not acceptable. Appropriate limitations should be placed on the use of adjunctive topical therapies, including the use of antiseptics.

The number of lesions should be counted and an estimate made of the total body surface affected. Protocols may set limitations on numbers and/or surface area, especially if treatment is topical. For topical treatments, the protocol may designate the largest lesion, a specific number of lesions or all lesions to be assessed for outcome. Depending on the strategy adopted, pre-defined additional analyses may be needed by lesion number or area since untreated neighbouring lesions can affect the likelihood of clinical success at treated lesions.

In the specific case of impetigo, for which the characteristic clinical picture is unlikely to occur as a result of other conditions, it could be acceptable to conduct the primary analysis in the full analysis set (ITT population), in which case an analysis of efficacy in all patients with a pathogen (microbiological-ITT) should be a pre-defined secondary analysis. Clinical resolution should be assessed at a post-therapy visit and at a later follow-up visit to document relapse rates. It is recommended that pathogens recovered from lesions that have not resolved by end of treatment or which relapse should be investigated for susceptibility to the test antibacterial agent and for production of toxins.

Infected atopic dermatitis

This occurs predominantly in pre-pubertal paediatric patients. A demonstration of efficacy in other types of infected dermatoses cannot be extrapolated to infected atopic dermatitis because it has a specific underlying pathophysiology requiring different management compared to some other superficial dermatoses.

A non-inferiority study against a licensed systemic or topical treatment (selected to enable a double-blind study design) is considered acceptable provided that strict inclusion criteria are used. The suggested non-inferiority margin is -10%. The use of adjunctive therapies such as topical steroid treatment and the use of occlusion should be standardised in the study protocol.

As part of the eligibility criteria, the size of the infected portion of the lesion or lesions should be predefined and, in case of topical treatment, the disease should be amenable for treatment by this route of administration.

Since a clinical picture suggesting super-infection is not always due to secondary bacterial infection, it is recommended that the primary analysis is conducted in all patients with a pathogen, with a pre-defined secondary analysis in the full analysis set. Clinical success should be based on the resolution of signs such as crusting, weeping/exudation, pustule formation and purulent discharge. A demonstration of non-inferiority could be based on comparison of clinical success rates at a visit timed from randomisation to occur at post-therapy days 7-9. Clinical resolution should also be assessed at a later visit to document relapse rates.

Acute otitis media (AOM)

This occurs most often in children aged less than 5 years. Whilst AOM also occurs occasionally in older children and adults, the underlying causes and pathogens may vary. Furthermore, the use of active antibacterial treatment has not been established to be superior to no treatment in children aged > 5 years.

Children aged < 3 years

It is considered that published data support acceptance of a non-inferiority trial design in a patient population that is aged from 6 months to 3 years, has adequately defined AOM and when the comparator is oral amoxicillin-clavulanate administered at the highest dose that is approved for treatment of AOM in this age group across the study sites and for at least 7 days. The available data do not provide, however, an unequivocal indication of the primary endpoint and non-inferiority margin to apply. Sponsors are advised to discuss the non-inferiority margin that might be acceptable with EU Competent Authorities.

It is recommended that all eligible children should present with acute onset (within 48 hours) otalgia and a bulging tympanic membrane on otoscopy as a minimum. AOM may be unilateral or bilateral and stratification is suggested. All signs and symptoms compatible with an ongoing acute infection should be documented and the use of a scoring system is recommended.

Clinical success should require resolution of abnormalities on repeat otoscopy (in both ears if AOM was bilateral) and resolution of otalgia. There should also be resolution of signs and symptoms of an ongoing acute infectious process that were present at baseline. A demonstration of non-inferiority could be based on comparison of clinical success rates at a visit timed from randomisation to occur at 1-2 days post-therapy. There should also be a comparison of sustained success rates at approximately 14-21 days post-randomisation, depending on the length of treatment and timing of the TOC visit.

Children aged ≥ 3 years

At the current time an approval for treatment of AOM in other age groups and/or in populations that do not meet these diagnostic criteria is not possible based on non-inferiority studies. Alternative study designs to assess treatment of AOM in which the tympanic membrane is intact include a demonstration of superiority vs. placebo or vs. no treatment, in which case criteria for institution of rescue therapy should be pre-defined in protocols.

Acute group A streptococcal (GAS) pharyngo-tonsillitis

This can occur at any age but the eradication rate of GAS in paediatric patients with pharyngo-tonsillitis treated with penicillin has been reported to be lower than that in adult patients, giving uncertainty regarding the extrapolation of efficacy of other antibacterial agents between age groups.

A non-inferiority study against phenoxymethylpenicillin or against an aminopenicillin is considered acceptable.

Eligible subjects should have an acute onset sore throat (preferably recorded using a scoring system) and a positive rapid antigen detection test (RADT) or a positive culture for GAS. For patients enrolled on the basis of a RADT, a pharyngeal specimen should be obtained for culture confirmation of GAS and only those patients with a positive baseline culture should be eligible for the primary analysis. A secondary analysis should be conducted in all patients with a positive RADT or culture.

The primary endpoint should be the microbiological eradication rate based on cultures obtained at the test-of-cure visit, conducted at around 5–7 days post-therapy.

Sponsors are advised to discuss the non-inferiority margin that might be acceptable in the age subgroup to be enrolled with EU Competent Authorities but in all cases it is recommended that it must not exceed 10%. A follow-up visit occurring at approximately 38 to 45 days post-randomisation should be planned to assess relapses and any complications of the infection.

Acute haematogenous osteomyelitis (AHO)

This has a different presentation to other forms of osteomyelitis that can occur in adults and children (e.g. due to trauma and/or around prosthetic implants) and may require a different duration of treatment.

In AHO, a non-inferiority trial is acceptable but available data do not provide an unequivocal indication of the non-inferiority margin to apply and it is recommended to discuss the margin with EU Competent Authorities. Comparative antibacterial regimens should be selected to cover the most likely pathogens based on local experience of AHO cases and the age of the child.

Patients may be enrolled based on the clinical picture, imaging studies and microbiological findings (e.g. Gram's stain and/or a rapid diagnostic test). The protocol should list criteria to be met to confirm the diagnosis and to define the primary analysis population accordingly.

The primary endpoint may be based on a measure of clinical improvement from baseline in pain, inflammation and limb function on day 8-post randomisation. The primary analysis based on the clinical improvement endpoint should be supported by a secondary analysis of the rate of clinical cure (which is likely to exceed 90%) judged at an appropriate time point (e.g. 21-35 days after end of therapy). It is strongly recommended that an independent Data Adjudication Committee unaware of treatment assignments is appointed to confirm AHO cases and to assign clinical outcomes to be used in primary and secondary analyses.

Patients should be followed for 6 months from study entry for relapse since progression to chronic osteomyelitis or relapse almost always occurs within this timeframe.

7. Safety aspects

Regardless of the route of administration, the safety profile will be driven mainly by the systemic exposure to the antibacterial agent. For the most part, a similar safety profile is expected across age subgroups when similar systemic exposures (Cmax and AUC) are achieved using the proposed dose regimens. Additional safety considerations apply to injectable and topical treatments, including issues such as local tolerability (e.g. at the infusion site or on treated surfaces).

Safety data may need to be generated in the paediatric population or in specific age subsets if there are emerging concerns from the available non-clinical and/or clinical data that are especially relevant to the paediatric population (e.g. age-specific adverse effects such as those of fluoroquinolones). In

these instances, the need to adequately document safety in children has implications for the size of the pre-approval paediatric safety database that should be addressed in the paediatric investigation plan.

Any uncertainties related to extrapolation of safety at the time of seeking approval for use in paediatric age subgroups should be discussed in the application dossier and appropriate post-marketing measures should be proposed to collect safety data in the paediatric population, particularly when the size of the pre-approval safety database is very limited.

Safety data should be described for the overall paediatric population and, if the number of subjects allow it (e.g. if a demonstration of efficacy in paediatric patients is required), by age sub-groups.

A late-follow up visit will usually be needed to document the outcome of adverse reactions. Long term follow-up for safety is not expected for most antibacterial agents that are administered for a limited period unless signals of concern have been shown in non-clinical studies (particularly if observed in juvenile animals) that would not preclude paediatric development but raise issues that cannot be addressed by further nonclinical studies or by the existing clinical safety data. The exact duration of follow-up in these situations should be decided on a case-by-case basis.

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