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Assessment report

Review under Article 5(3) of **Regulation (EC) No 726/2004**

Anti-tuberculosis medicinal products containing isoniazid, rifampicin, pyrazinamide, ethambutol, rifabutin: posology in children

Procedure no: EMEA/H/A-5(3)/1310

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Request for CHMP opinion

Recently published data on the pharmacokinetics of the major paediatric anti-tuberculosis medicines (isoniazid, rifampicin, pyrazinamide and ethambutol) (1,2,3,4) point to the fact that the current treatment recommendations included in the product information of medicinal products authorised across European Member States are no longer accurate.

In July 2008, the World Health Organisation (WHO) recognised this issue and organised a meeting with a group of paediatric pharmacology and tuberculosis (TB) experts. The group recommended changes to the dosing regimen of major drugs as well as the need for development of fixed dose combination products. More specifically, the group recommended increase of the dosing of the anti-tuberculosis medicinal products in children due to concerns of under-dosing and the development of resistance, and identified future research areas to define the appropriate fixed dose combinations.

On 17 June 2011, the French Medicines Agency (Afssaps) presented to the European Medicines Agency a request for a CHMP opinion under Article 5(3) of Regulation (EC) No 726/2004 on the optimal dosing regimen for the first line anti-tuberculosis medicinal products containing isoniazid, rifampicin, pyrazinamide, ethambutol and rifabutin in the paediatric population.

The multi-resistance was not addressed in this procedure.

2. Scientific discussion

2.1. Introduction

Tuberculosis (TB) is still a major global health problem for paediatric population, despite the efforts in the past decades to bring the problem under control. The risk for progression from the infection stage to the disease is particularly high in certain paediatric subsets (children under 5 years of age and adolescents) (5). In addition, if TB progresses from infection to disease, this is severe in children. Extrapulmonary TB is more often present in the paediatric population. Although most cases are found in the developing countries, where diagnosis is usually made at an advanced stage of the disease, active TB is still prevalent in some of the EU Member States.

It is currently widely accepted that the mainstay of tuberculosis therapy in the paediatric population is to ensure dosage regimens that yield similar exposure to that in adults (6). However, pharmacokinetic (PK) data in children were scarce or unavailable at the time dosing information was established. The choice of the initial therapeutic regimen in childhood TB depends on a number of factors which are described in detail in the WHO Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children (7).

The most common used medicinal products for initiating TB therapy in children are isoniazid (INH or H), rifampicin (RMP or R), pyrazinamide (PZA or Z) and ethambutol (EMB or E), which along with rifabutin are considered as “first line therapy”.

Administration of insufficient or excess doses poses important health care risks, including development of resistance to anti-TB medicines, or safety concerns. This is especially important taking into

consideration the current difficulties of treating multi drug resistant (MDR1[i])- and extended drug resistant (XDR2[ii]) tuberculosis.

Recently published data on the pharmacokinetics of the major paediatric anti-TB medicines (isoniazid, rifampicin, pyrazinamide and ethambutol) (1,2,3,4) point to the fact that the current treatment recommendations included in the product information of medicinal products authorised across European Member States are no longer accurate.

In July 2008, WHO recognised this issue and organised a meeting with a group of paediatric pharmacology and TB experts. The group recommended changes to the current dosing regimen of first line therapies as well as the need for development of fixed dose combination products and more specifically recommended increase of the dosing of the anti-tuberculosis medicinal products in children due to concerns of under-dosing and the development of resistance, and identified future research areas required to define the appropriate fixed dose combinations.

In June 2011, the AFSSAPS considered that in view of the important health care issues associated to the administration of insufficient or excess doses of authorised anti-TB Medicinal products for the treatment of tuberculosis in children, it was important that the signal raised by WHO towards an inadequate regimen in children be taken into account for revising the heterogeneous recommended regimen for the EU medicinal products to ensure an optimal therapeutic management of first line tuberculosis in children.

It is anticipated that once homogeneous dosing regimen in children will be achieved across EU, applicants might be more inclined to develop fixed dose combination which are of critical need in view of adherence issues especially in the paediatric population.

This is the purpose of this review that consists in discussing to what extent the 2008 WHO dosing recommendation could be used for EU harmonisation of dosing in children.

In order to have a clear picture on the WHO dosing recommendation on first line TB the following table is provided:

Drugs alone	**2006 WHO recommendations** Adult & children	**2008 WHO recommendations** Children
RMP	10 (8-12) mg/kg	15 (10-20) mg/kg
INH	5 (4-6) mg/kg (max 300 mg)	10 (10-15) mg/kg
PYR	25 (20-30) mg/kg	35 (30-40) mg/kg
EMB	adult 15 (15-20) mg/kg children 20 (15-25) mg/kg	20 (15-25) mg/kg

[i] *MDR Tuberculosis is defined as bacteria resistant to at least isoniazid and rifampicin*

[ii] *XDR Tuberculosis is defined as bacteria resistant to isoniazid and rifampicin (i.e. MDR-TB) as well as any fluoroquinolones and any of the second line anti-TB injectable drugs (amikacin, kanamycin or capreomycin)*

2.2. Discussion

2.2.1. Isoniazid (INH)

Isoniazid is a bactericidal agent active against organisms of the genus Mycobacterium, specifically *M. tuberculosis*, *M. bovis* and *M. kansasii*. It is a specific agent, ineffective against other micro-organisms. Isoniazid is bactericidal to rapidly-dividing mycobacteria, but is bacteriostatic if the mycobacterium is slow-growing. Oral doses of INH are rapidly absorbed and readily distributed throughout the body.

As regards the safety profile of the drug, it is mainly characterized by hepatotoxicity and neurotoxicity.

Based on the limited literature data substantiating the risk in children, hepatotoxicity is reported in children treated for prophylaxis of TB (INH alone) or for active TB (combined with rifampicin). In safety textbooks (Drugdex and Martindale), the incidence of hepatotoxicity in children is mentioned as rare and less frequent during prophylaxis treatment than curative treatment. No clear dose-toxicity relation for INH-induced hepatotoxicity has been established.

Main neurotoxicity effects (ataxia, convulsions, dizziness, tinnitus, encephalopathy, neuropathy, psychosis…) are described as being dose-dependent and occurred mostly in patients with central nervous system (CNS) medical history. Peripheral neuropathy in some cases irreversible is the most frequent adverse effect of INH neurological effect. Thus, in order to avoid the occurrence of peripheral neuropathy especially in human immunodeficiency virus (HIV)-infected patients or patients with nutritional deficiency, it is recommended during TB treatment to add a supplementation of pyridoxine (vitamin B6).

Based on the WHO literature review on PK data and on published data, it can be stated that T>MIC (Minimum Inhibitory Concentration) has been chosen as a predictive factor of clinical efficacy with MIC= 0.025-0.05 µg/ml. The therapeutic range of serum concentrations is approximately 3 µg/ml to be maintained at least 6 hours.

In TB meningitis, higher doses of INH are to be used to cover the eradication of mycobacteria present within the caseous tissue surrounding the base of the brain.

Younger children are exposed to lower concentrations of INH than older children receiving equivalent mg/kg body weight doses, and also in comparison to adults. However, there is very little data for infants in particular those < 3 months; studies in South Africa on low birth weight infants are currently ongoing but data are not yet available.

Optimal concentration issue

As regards the signal towards the inadequacy of the WHO 2006 recommended 5 (4-6) mg/kg in children, and in addition to the WHO expert meeting review, the increase of the INH dosing recommendation in children appears to be required.

Several studies (8,9,10) report the need for increasing INH dose in children, having in mind that the therapeutic range of serum concentrations is of approximately 3 µg/ml to be maintained at least 6 hours:

- Study in children with severe forms of TB showing that 4-6 mg/kg were insufficient to achieve comparable peak concentrations to a 300 mg dose in adults (receiving a dose of 5 mg/kg/day). To achieve adults' concentrations, 8-12 mg/kg were judged necessary (8).
- Study in children from 0 to 13 years suggesting the need for increasing INH dose to at least 10 mg/kg in children < 5 years to ensure that the faster acetylators of INH are exposed to

adequate serum concentrations (9). This study confirmed also the trimodal model of INH elimination in children i.e. homozygotous slow acetylators SS, heterozygotous fast acetylators (intermediate) FS and fast homozygotous acetylator FF, F and S being co-dominant.

- Study in children with 68% aged of < 10 years treated for meningitis showing that 4 mg/kg was insufficient to obtain such concentrations both in serum and cerebrospinal fluid (CSF) (10).

However, some studies report successful results in children > 5 years treated with 5 mg/kg/day INH, especially when administered with other anti-TB drugs. One of these studies permitted to elaborate a graph correlating bodyweight with INH dose and leading to recommend decreasing doses according to increasing age (11). Another study (12) confirmed previous data showing a higher acetylation index in children compared to adults and clearly pointed the influence of age in the INH PK especially in slow acetylators.

Nevertheless, some data suggest that the use of high doses (>10 mg/kg) could not be beneficial. When considering the potential need for increasing the dose, the optimal balance between efficacy and safety should be taken into account.

Indeed several authors have questioned whether the high dosages of INH commonly used in paediatric practice for the treatment of pulmonary TB and meningitis are really necessary. They warn against going beyond 10 mg/kg in children, even in case of meningitis, based on the possible neurotoxicity and/or hepatotoxicity (13,14). The clear evidence of hepatic overload in patients, especially in children (< 3 years), was established and considered to be due to the relative immaturity of their hepatic functional capacity.

Moreover, the data suggest that at approximately 3 hours after dosing, the cerebrospinal fluid (CSF) INH concentration equals the plasma concentration irrespective of dosage or inactivation type so that measurements of the plasma INH concentration at this point will be a reasonably reflection of the CSF concentration.

Factors influencing the INH PK

- Age is reported as being a factor influencing INH PK:
    - INH is more rapidly metabolized in children than in adults owing to a probable higher liver weight/body weight ratio and to a more pronounced first pass effect (< 5 years)
    - The maturation of the N-acetyl transferase 2 (NAT2, enzyme involved in INH metabolism) occurs during the first 4 years of life
    - Relative immaturity of hepatic functional capacity in children (<3 years).
- Acetylation status appeared to be a prominent determinant of INH concentrations in adults and children (fast / intermediate / slow).
    - However, it is acknowledged that the relative therapeutic disadvantage of the heterozygote fast acetylator will be concealed by the synergistic potential of a multidrug regimen.
    - Although data highlight the influence of acetylation status on INH PK, the NAT2 genotyping is not recommended in routine, because it is believed that higher doses in young children will cover the fast acetylation status patients with potential suboptimal doses (9).
- Body surface area (BSA) is promoted by some authors (11) as it appears more appropriate to determine the correct dose in children. Indeed, this appears to be a more appropriate way to obtain INH concentrations with less variability especially among young children. BSA could be

more appropriate to determine the correct dose in obese children. On the other hand, there are established (and newly developed) anthropometric approaches to determine body weight which appear to be accurate for the purpose of use in determining drug dose.

- Food intake influences INH bioavailability. It is recommended that INH is taken without food and at least 30 minutes before any meal.
- Malnutrition did not seem to affect the gastrointestinal absorption (15,8).
- No apparent influence of the HIV-infection status on INH PK had been observed. HIV co-infection seems to have no impact of INH PK (8).
- The interval of administration of anti-TB on a daily basis or twice-/thrice-weekly may have an influence on the global management of TB treatment with the consequences of a lack of compliance in case of intermittent therapy leading to a risk of sub-therapeutic concentrations of anti-TB drugs. Lower doses in intermittent regimen in the situation of TB meningitis where a risk of a drug-induced hepatotoxicity (such as INH) is higher, should be considered to be as efficacious and more acceptable than daily regimen (16).
- The formulation of INH has also an influence on the PK of INH in children. It had been demonstrated that syrup produced the highest peak concentration compared to the crushed tablet or the parenteral solution (17). Especially to facilitate the compliance in children, suspension formulation should be encouraged as it has better PK parameters compared to other formulations.

Overall conclusion

In 2008 WHO increased the INH recommended dosing from 5 (4-6) mg/kg to 10 (10-15) mg/kg in children.

Existing pharmacokinetic data for INH in infants and children and generally accepted PK-based pharmacodynamic surrogates would not appear to support a reduction in dose to 5 mg/kg in children greater than 5 years of age. This would be especially true for individuals with a NAT2 “fast acetylator” phenotype where a daily dose < 10 mg/kg would produce plasma concentrations far less than 40% of the dosing interval. Given the apparent high therapeutic index of INH as it relates to the current WHO dosing recommendations, a lowering of the dose (to 5 mg/kg) for older children could produce significant systemic underexposure with its possible attendant therapeutic problems (e.g., increased INH resistance, sub-therapeutic exposure at a tissue level).

On the other hand, younger children are definitely exposed to lower concentrations of INH and a dose of at least 10 mg/kg of INH in children less than 5 years appears necessary to ensure that the faster acetylators of INH are exposed to adequate serum concentrations of INH (above 1.5 µg/ml 3 hours after INH administration).

Although data highlight the influence of acetylation status on INH PK, the NAT2 genotyping is not recommended in routine.

In conclusion, the CHMP, acknowledging that

- determining the optimal dose of INH is difficult (mainly driven by acetylator status which is not determined in routine)
- there are limited data to specifically tailor the dose depending on the age strata in children (to cover the differential enzymatic maturation)
- under-exposure should be avoided

concurred with the WHO dose recommendation of 10 mg/kg INH with a range of 10-15 mg/kg, except with regard to the dosing in infant less than 3 months where no recommendation can be made due to the lack of data in this population.

2.2.2. Rifampicin (RMP)

Rifampicin has bactericidal activity in vitro against slow and intermittently growing *Mycobacterium tuberculosis* organisms by inhibition of the Deoxyribonucleic acid (DNA)-dependent Ribonucleic acid (RNA) polymerase activity in susceptible *M. tuberculosis* organisms.

Rifampicin is easily absorbed from the gastrointestinal tract and widely distributed throughout the body. Food consumption inhibits absorption from the gastro-intestinal (GI) tract, and the drug is more quickly eliminated.

It is admitted that the therapeutic range of serum concentrations is approximately 10 µg/ml and AUC/MIC ratio (Area Under the Curve/Minimum Inhibitory Concentration) to be the best PK/PD parameter (Pharmacokinetic/Pharmacodynamic) predictive of clinical efficacy for RMP with MIC = 0.5 µg/ml.

It is well characterized that the salient aspect of the safety profile of RMP is hepatotoxicity. The most severe adverse effects are observed in intermittent treatment or after resuming a previous treatment.

In reference safety textbooks (Drugdex and Martindale), attention is drawn on rifampicin/pyrazinamide combination used for prophylaxis in latent TB due to the potentially high risk of hepatotoxicity but no clear dose-dependence is mentioned.

In addition, fever, gastrointestinal disturbances, rashes, and immunological reactions such as thrombocytopenia, acute renal impairment and influenza-like syndrome, probably due to an immuno-allergic mechanism, account for frequent adverse events.

Optimal concentration issue

Pharmacokinetic findings of the WHO literature review underlined in infancy and childhood the continuous change in body weight, surface area, body composition and enzyme maturation implying special dose consideration in this population.

Based on the review in 2008, the recommended WHO RMP dosing has been increased from 10 (8-12 mg/kg) to 15 (10-20 mg/kg).

Following the conclusion of the WHO review and of some studies (18), 8-12 mg/kg RMP dosing appears to be insufficient as this range of doses documented very low RMP serum concentrations in children.

It has to be underlined that some articles report that a minimal dose of 12 mg/kg should be necessary to obtain therapeutic concentrations in the serum (19,20) and that the highest limit of the RMP dosing should be fixed to 15 mg/kg, considering it as sufficient to allow RMP passage in CSF (21).

However, referring to the adult dosing regimen and the fact that in children with severe form of tuberculosis meningitis dosage of 20 mg/kg might be required to maximize efficacy, the CHMP could concurred with the WHO dosing recommendation.

With a dosing range of 10 to 20 mg/kg/day, clinicians would be able to engage clinical considerations (e.g., disease severity) with regard to dose selection to initiate therapy and still remain in this range.

Factors influencing the RMP PK

- Age appears to be one of the most important sources of concentration variation in children. Doses higher than 10 mg/kg/day have to be used in children in order to attain the adequate concentration (22,23,24).
- Body surface area (BSA) appears as being a better criterion as serum and urine levels differences between adults and children seem to be closely related to the differences in the body water compartments (larger volume of distribution in infants). Indeed, BSA could be more appropriate to determine the correct dose in obese children. On the other hand, there are established (and newly developed) anthropometric approaches to determine body weight which appear to be accurate for the purpose of use in determining drug dose (22,24).
- HIV infection status: no evidence of differences in RMP concentrations between the HIV-infected and HIV-uninfected children is reported. However, drug-drug interaction is a challenging issue with most antiretroviral agents.

Overall conclusion

In 2008 WHO increased the RMP recommended dosing from 10 (8-12) mg/kg to 15 (10-20) mg/kg in children.

Although some articles were in favour of increasing the lower bound from 10 to 12 mg/kg and some in favour of setting the highest dose for severe forms of TB at 15 mg/kg, the targeting 15 mg/kg with a minimum dose of 10 mg/kg (notably in case of malnutrition) and a maximum dose of 20 mg/kg (for the most severe TB forms such as meningitis) as recommended by WHO appears to be an adequate range of doses.

Regarding dosing in infants less than 3 months, additional pharmacokinetic data for rifampicin are needed to establish a dosing recommendation.

2.2.3. Pyrazinamide (PZA)

Pyrazinamide may be bacteriostatic or bactericidal against *Mycobacterium tuberculosis* depending on the concentration of the drug attained at the site of infection. The mechanism of action is unknown. *In vitro* and *in vivo* the drug is active only at a slightly acidic pH.

PZA is well absorbed from the GI tract and widely distributed in body tissues and fluids including the liver, lungs and CSF. PZA is well absorbed orally. It crosses inflamed meninges and is an essential part of the treatment of TB meningitis.

The salient aspect of the PZA is the hepatotoxicity. Data have suggested the hepatotoxicity of PZA to be dose-dependent. Based on the WHO literature review, safety data were issued from only two articles (25,26). Other adverse effects (nausea, sickness, diarrhoea, pruritus, blurred vision, joint pain, digestive pain) are reported as being more frequent in adults than in children, in HIV-infected patients than in HIV-uninfected.

In the reference safety textbooks (Drugdex and Martindale), attention is drawn on rifampicin/pyrazinamide combination regarding the high risk of hepatotoxicity due to the synergism of 2 drugs and PZA effects on uric acid metabolism was also mentioned with more frequent hyperuricaemia with daily treatment than with intermittent regimen.

As compared to isoniazid, rifampicin and ethambutol, PZA appears to follow one compartment kinetics and to have the most predictable pharmacokinetic profile based on a review of existing published pediatric data.

Optimal concentration issue

Based on the WHO review and literature (25), it is admitted that the therapeutic range of serum concentrations is approximately 20 µg/ml.

The available PK data in children (27,28,29) support an increased dosing regimen from 25 mg/kg to 35 mg/kg, as recommended by WHO since 2008.

Factors influencing the PZA PK

- Age appears to have a considerable impact on PZA PK especially in young age (30).
    - Young age tends to be associated with lower Cmax (maximum plasma concentration), especially with lower concentration of PZA in younger children (0-4 years) compared to older children (31).
    - A dose of 30 mg/kg might allow to cover the differences. Indeed, some results showed that serum levels after an oral dosage of 30 mg/kg do not differ between all age group up to the age of 14 years regardless of whether PZA is given alone or in combination with INH and RMP (28). Children appeared to absorb more slowly but eliminated PZA more quickly than adults, especially in 6-12 years of age (25).
    - A higher dose in all age groups of children should be recommended to cover the lower concentrations in younger children.
- The nutritional status (30) has been regarded as a potential factor with an impact on PZA PK. No significant relation was found between malnutrition and PZA PK (29,31).
- HIV infection status could affect PZA absorption. Conflicting results deserve new studies with a larger number of children of different age and genetic background to better define the doses of PZA appropriate for children (29,31).
- PZA concentrations appear to be related to body weight rather than body surface area (28).
- The rhythm of administration should be regarded also as a potential factor of PK variation in PZA serum levels (30,31).
- Food interaction on PZA PK is described with negligible effect on Cmax and AUC but reduced absorption was reported occurring when PZA and EMB were given with a meal especially high-fat meal. Minimal effects of food and antacids on PZA absorption have also been described (25,31).

Overall conclusion

In 2008 WHO increased the recommended PZA dosing from 25 (20-30) mg/kg to 35 (30-40) mg/kg in children.

The highest dose of 40 mg/kg would be required for severe forms of TB such as meningitis (32). Any data indicate an increased hepatotoxicity in children associated with higher PZA dosages.

Based on the WHO review and literature, the CHMP recommends an increase of PZA dosing regimen from 25 (20-30) mg/kg to 35 (30-40) mg/kg.

Regarding dosing in infant less than 3 months in line with WHO in 2008, no recommendation can be made as there is still a lack of data in this population.

2.2.4. Ethambutol (EMB)

Ethambutol was not part of the 2008 WHO review, but for the completeness of the current review, on the adequate dosing in children for first line anti-TB, this product has been addressed as well.

Ethambutol has been shown to be effective against strains of *Mycobacterium tuberculosis*. EMB is bacteriostatic against actively growing TB bacilli, with an activity on extra- or intracellular *M. tuberculosis*. Ethambutol distributes widely into body fluids and tissues.

Resistance develops rapidly if ethambutol is used alone. It seems to develop in a step-wise manner and may be delayed or prevented by using ethambutol in combination with other anti-tuberculosis agents. Cross-resistance has not been reported with other anti-tuberculosis agents.

Ethambutol distributes widely into body fluids and tissues.

It is admitted that the therapeutic range of serum concentrations is approximately 2 µg/ml.

Optimal concentration issue

Existing pharmacokinetic data on EMB are sparse in comparison to INH, RIF and PZA and suggest large variability in the dose.

Efficacy of EMB is time-dependent and thus the duration of effective serum levels has to be considered. Prolonged T>MIC is required as EMB is a bacteriostatic agent and its main function in a multidrug regimen is to protect the companion drugs against resistance particularly in the face of INH resistance.

As regards safety, ocular toxicity is the salient aspect of the safety profile.

In the reference safety textbooks (Drugdex and Martindale), optic neuritis is the main adverse effect to be mentioned for EMB with a clear dose and treatment duration /effect dependent. Its incidence is 1% after administration of 15 mg/kg/day, 6% after 25 mg/kg/day and 15 % after 35 mg/kg/day, mostly occurring after 2 months of treatment and generally reversible. It is to be noted that some cases of irreversible blindness had been reported. This ocular toxicity had been more frequent in daily treated patients than in intermittent regimen.

Based on the WHO review, 2 articles (33,34) mentioned safety data mainly focusing on ocular toxicity which appears to be dose-dependent in adult. No case has been observed in children in the first article. The literature review of EMB use in children (33,34) showed only 2/3811 children with ocular toxicity i.e. 0.05% of incidence when treated with EMB doses from 15 to 30 mg/kg. In the second article, this incidence increased to 0.7% in 4/567 children from 2-14 years receiving 35 mg/kg. Rare EMB toxicity is due to the considerably low serum concentrations reached in children.

Some data (34,35,36) speak in favour of upgrading the range to achieve the minimal serum concentration level of 2 µg/ml, 20 mg/kg and all the more 15 mg/kg might not be sufficient. The dosage of 25 mg/kg seems to be sufficient in the age group of 10-14 years whereas for the age group of 2-<6 years and 6-<10 years, a dosage of 35 mg/kg might be necessary for therapeutic efficacy and to be used preferably also in case of INH- or RMP resistant TB.

In view of published PK-based pharmacodynamic surrogates for EMB, existing PK data would initially appear to support the need for a daily dose in the range of 25 to 35 mg/kg to increase the likelihood that optimal systemic exposure is achieved. Despite this apparent pharmacokinetic “justification”, concern regarding the possible relationship between serious ocular toxicity and systemic EMB exposure appears justified.

Factors influencing the EMB PK

- Age is also for EMB a source of variability in plasma concentrations (32,36).

- Malnutrition seems not to impact on EMB PK when combined with PZA which presented lower serum levels in malnourished children while EMB levels were not (31).
- Body surface area (BSA) could be a better criterion to produce therapeutic serum levels in all age groups, leading to a high efficacy of anti-TB treatment without increased ocular toxicity as dosages based on body weight caused sub-therapeutic serum levels (34). BSA could be more appropriate to determine the correct dose in obese children. On the other hand, there are established (and newly developed) anthropometric approaches to determine body weight which appear to be accurate for the purpose of use in determining drug dose.
- HIV infection can not be considered as a source of EMB PK variation as one study (31) in HIV-infected children showed that PZA and EMB concentrations were not significantly lower in HIV-infected children compared to HIV-uninfected. However conflicting results were also observed with EMB absorption, distribution and elimination influenced by age and to a lesser degree by HIV status (36).
- The interval of administration should be regarded as a potential factor of PK variation in EMB serum levels, especially in young children as illustrated in literature (31,36).

Overall conclusion

In 2008, WHO has not reviewed the previously settled posology of EMB (20 (15-25) mg/kg).

Weight based dose in children in 2006 were already higher than those of adults and therefore have remained unchanged further to the 2008 WHO review. In 2006, it was indeed already identified that the PK was different between adults and children.

Although some existing PK data appear to support the need for a daily dose in the range of 25 to 35 mg/kg, concerns regarding the possible relationship between serious ocular toxicity and systemic EMB exposure appear justified. Moreover, it is acknowledged that the anti-TB activity in fully sensitive strain will be mainly driven by INH and rifampicin, therefore the dose range could be sufficient.

In the case of managing multi-drug resistant (MDR) disease, there is a much stronger case to be made for moving to the higher end of the dosing range, but where specialists are available to monitor for ocular toxicity.

Overall, the CHMP could concur with the WHO dosing recommendation for EMB dosing of 20 (15-25 mg/kg). It is acknowledged that in multi-resistant TB (out of this scope), higher doses could be required; however, this is to be handled on a case by case basis with specialists in the field.

Regarding dosing in infant less than 3 months in line with WHO in 2008, no recommendation can be made as there is still a lack of data in this population.

2.2.5. Rifabutin

Rifabutin was not part of the 2008 WHO review, but for the completeness of the current discussion on the adequate dosing in children for first line anti-TB, this drug has been addressed as well. Indeed, it might be used in EU countries to handle drug-drug interaction in HIV co-infected patients. However, its activity on *Mycobacterium tuberculosis* is known as being lower than rifampicin.

Rifabutin is an antibiotic that inhibits DNA-dependent RNA polymerase activity in susceptible cells. It is bactericidal. Because of rapid emergence of resistant bacteria, use is restricted to treatment of mycobacterial infections and a few other indications.

Rifabutin is well absorbed when taken orally and is distributed widely in body tissues and fluids, including the CSF.

Adverse effects were similar to those observed in the adult population and included leucopenia, neutropenia, and rash. In addition, corneal deposits have been observed in some patients during routine ophthalmologic surveillance of HIV-positive paediatric patients receiving "Mycobutin" as part of a multiple-drug regimen for MAC prophylaxis. These are tiny, almost transparent, asymptomatic peripheral and central corneal deposits which do not impair vision.

Doses of rifabutin may be administered mixed with foods such as applesauce.

Optimal concentration issue

Two publications reviewed the PK parameters of rifabutin in children:

- One (37) comparing PK parameters of rifabutin and rifampicin presented the PK parameters of rifabutin and its pharmacological characteristics. It has been showed that Cmax of rifabutin is ~10-fold lower than that of rifampicin and the elimination half-life ($t_{1/2}$) is ~10-fold higher.
    - In children, the rifabutin PK parameters appeared to be similar to those in adults and the adverse effects as well.
    - The minimum effective dose and the optimal dose of rifabutin for prophylaxis for most mycobacterial infections are not known.
- In the second publication (38), it has been showed that food decreases the rate of absorption; the drug can be mixed with food such as applesauce for administration to children.
    - The pharmacokinetics of rifabutin in children is reported to be similar to that in adults, but $T_{1/2}$ appears to be slightly shorter in children.
    - It has been observed the development of uveitis in case of 600 mg/day in a child infected with HIV in combination with ethambutol and clarithromycin.
    - The recommendation following this study is to establish rifabutin for prophylaxis only if the patient does not have active TB to avoid the development of resistance to rifampicin in *M. tuberculosis*. Rifabutin should not be administered concurrently with either ritonavir (or nelfinavir) because they may lead to decreased concentrations of these drugs as well to increased concentrations of rifabutin.

Overall conclusion

Paediatric pharmacokinetic data for Rifabutin are too limited to enable reasonable data-driven projection of an appropriate paediatric dose.

In addition, the CHMP could not provide any recommendation with regard to the dose of rifabutin to be used in HIV co-infected children due to a lack of paediatric pharmacokinetic data.

2.2.6. Need for appropriate Fixed-Dose Combinations

Fixed Dose Combinations (FDCs) are of critical need in view of adherence issues especially in the paediatric population.

In 2008 the WHO expert meeting decided upon the following appropriate formulation: Isoniazid 100 mg / Pyrazinamide 350 mg / Rifampicin 200 mg (/ Ethambutol 200 mg).

In the WHO expert meeting report, it was stated that the medical need for FDC is not fulfilled.

Appropriate FDC according to WHO

An appropriate FDC would be a 3-drug FDC that allows for ethambutol to be added as appropriate.

FDC	Adult & >6 years, >30 kg	WHO ideal paediatric formulation
RMP	10 (8-12) mg/kg	20 mg/kg highest range
INH	5 (4-6) mg/kg	10 mg/kg mean range
PYR	25 (20-30) mg/kg	35 mg/kg mean range
EMB	15 (15-20) mg/kg	20 mg/kg mean range

Manufacturers have proposed FDC's that exclude rifampicin and isoniazid, the latter due to technical complications in manufacturing; however, this does not appear consistent with established clinical needs or the benefits of an FDC.

Identified limitations for FDCs

- Formulation and manufacture of FDCs: In the case that a 3- or 4-drugs FDC can be developed, studies indicate that investment in formulation work to create a stable dispersible tablet will be needed. Previous attempts to develop an appropriate tablet have resulted in products that could not be administered to paediatric patients.
- Lack of data: While numerous studies are under way, they have limitations in design or other issues that may make the information not useable or not timely for use in supporting a regulatory application.

Studies design for regulatory application

The CHMP concurred with the WHO proposed approach to substantiate the adequacy of a FDC; a bioequivalence study in healthy subjects of the FDC against respective loose combination with appropriate comparator products and a clinical study with pharmacokinetic data in the targeted paediatric population would be required.

Any development of FDC should be performed in accordance with the relevant EU guidelines. It is recommended to applicants to seek for a scientific advice beforehand.

3. Overall conclusion

Facing the clinical signals of sub-optimal exposure in paediatric population with similar weight based dosing regimen than the one used in adults, the World Health Organisation reviewed in 2008 its "Guidance for national tuberculosis programmes on the management of tuberculosis in children" to recommend an increase of the dose of the anti-TB medicinal products such as isoniazid, rifampicin and pyrazinamide.

The Committee considered the procedure under Article 5(3) of Regulation (EC) No 726/2004 initiated by the Afssaps to establish the optimal dosing regimen for the first line anti-tuberculosis medicinal products containing isoniazid, rifampicin, pyrazinamide, ethambutol and rifabutin in the paediatric population.

The Committee considered that, in view of the important health care issues associated with the administration of inaccurate doses of anti-TB medicinal products for the treatment of tuberculosis in children, the heterogeneous dosing regimens currently existing across the European Member States for

the first line therapies should be revisited in order to ensure an optimal therapeutic management of the tuberculosis in paediatric population.

Overall while acknowledging that the dosing regimen of first line Anti-TB therapies is difficult to define in children based on limited data available and several influencing factors (such as nutritional status, enzymatic maturity according to age …), the Committee agreed with the WHO current dosing recommendation in the paediatric population as follows:

Drugs alone	Dosing recommendation for children
Isoniazid (INH)	10 (10-15) mg/kg
Rifampicin (RMP)	15 (10-20) mg/kg
Pyrazinamide (PZA)	35 (30-40) mg/kg
Ethambutol (EMB)	20 (15-25) mg/kg

The upper range is indicated in case of severe form of the disease (meningitis).

The CHMP could not provide any recommendation with regard to the dose of rifabutin potentially to be used in HIV co-infected children due to a lack of paediatric pharmacokinetic data.

The CHMP acknowledged that data are currently insufficient to draw dosing recommendation in children below 3 months of age.

Multi-resistance was not addressed in this review.

Acknowledging the critical importance of adherence which is particularly challenging in children, the Committee would recommend the development of fixed dose combinations suitable for paediatric use on the basis of these dosing regimens in children.

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