Annex II

Scientific conclusions

Scientific conclusions

The treatment of bacterial infections is hampered worldwide by the global spread of multidrug-resistant (MDR) or extensively drug-resistant (XDR) Gram-positive and Gram-negative pathogens and the lack of development of new antibiotics active against such MDR and XDR bacteria. Therefore, the implementation of alternative treatment strategies such as the revaluation of older antibiotic agents is needed as a response to the development of antimicrobial resistance. In this context, interest in fosfomycin has grown in recent years in view of its unique mode of action and chemical structure that makes cross-resistance uncommon. This allows for additive and synergistic activities with other antibiotics. In addition, there are significant differences between the product information of fosfomycin-containing products across the European Member States, in particular in the approved indications and posology, that warrant harmonisation.

Overall, there is a need to revaluate the benefit-risk balance of the approved indications considering the current scientific knowledge. Furthermore, the appropriate dose and duration of treatment for oral, intravenous and intramuscular formulations need to be reassessed, as well as the adequacy of information on safety and pharmacological properties.

On 7 December 2018 the German National Competent Authority (Bfarm) triggered a referral procedure under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above elements on the benefit-risk balance of fosfomycin medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

Having reviewed all available data and taking into account the current clinical practice and current clinical guideline recommendations, the CHMP considered overall that fosfomycin still remains an important therapeutic option. The benefit-risk balance of the fosfomycin-containing medicinal products are detailed below.

Fosfomycin powder for solution for infusion

For fosfomycin powder for solution for infusion intended for intravenous administration the benefit-risk balance of the following indications, in all age groups, remains positive, when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment:

- **complicated urinary tract infections (cUTI)**

  Although clinical data for use of IV fosfomycin in cUTI are limited, CHMP concluded that fosfomycin IV has a positive benefit-risk balance in cUTI when considering these clinical data in combination with fosfomycin pharmacokinetic properties (in particular its distribution to kidney and bladder), its good *in vitro* activity against urinary (including MDR) pathogens and its acceptable safety profile.

- **infective endocarditis (IE)**

  Although efficacy data from clinical trials are limited, CHMP concluded that fosfomycin IV has a positive benefit-risk balance in the treatment of bacterial endocarditis when considering these clinical data in combination with fosfomycin pharmacokinetic properties, its good *in vitro* activity against causative pathogens and its acceptable safety profile.

- **bone and joint infections**

  The indication bone and joint infections is supported by sufficient clinical data. Furthermore, fosfomycin diffuses well into bone tissue reaching high concentrations and shows excellent activity against the main causative pathogens MSSA and MRSA and has an acceptable safety profile.

Therefore, the CHMP concluded that fosfomycin IV has a positive benefit-risk balance in this indication.

- **hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)**

  Nosocomial lower respiratory tract infections, respiratory tract infections and lung abscess were present among IV fosfomycin indications. There is general classification of pneumonia into HAP, VAP, and community acquired pneumonia (CAP) representing distinct entities.
  Lower respiratory tract infections (especially HAP/VAP) represent a life-threatening condition requiring rapid initiation of antimicrobial therapy.

  Even though the available clinical data supporting the use of fosfomycin in HAP/VAP come from uncontrolled or retrospective studies, when these data are considered in combination with its good penetration in lung tissue, the microbiological activity against lower respiratory tract pathogens and its acceptable and safety profile, the benefit-risk balance in this indication is considered positive by the CHMP.

  In contrast, no sufficient data is available to establish the efficacy of fosfomycin IV in the treatment of CAP. Therefore, the CHMP concluded that the benefit-risk balance of fosfomycin IV in this indication is negative.

- **complicated soft skin and tissue infections (cSSTI)**

  Although efficacy data from clinical trials are limited in the treatment of cSSTI , CHMP concluded that fosfomycin IV has a positive benefit-risk balance in this indication when considering these clinical data in combination with fosfomycin pharmacokinetic properties (in particular a good distribution into interstitial fluid of soft tissues), its good *in vitro* activity against causative pathogens for cSSTI and its acceptable safety profile.

- **bacterial meningitis**

  Among indications approved for IV fosfomycin CNS infections such as bacterial meningitis, meningitis, encephalitis and brain abscess were present.

  Clinical data on the use of fosfomycin for CNS infections are limited but taking in combination with PK data (good penetration across the blood–brain barrier) and PD (antimicrobial activity against relevant pathogens) properties of fosfomycin and its acceptable safety profile, the CHMP considered that the benefit-risk balance in this indication positive.

- **complicated intra-abdominal infections (cIAI)**

  Despite the limited evidence the CHMP considered the efficacy of fosfomycin IV established in the treatment of cIAI in combination with other antibacterial agents based on the available clinical data, the antibacterial spectrum of fosfomycin and its potential use for the treatment of surgically intractable intra-abdominal abscesses. Taking also into consideration its acceptable safety profile, the CHMP concluded that the benefit-risk balance of fosfomycin IV in this indication is positive.

- **bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above**

  Although there is a moderate clinical evidence for the efficacy of IV fosfomycin in the treatment of bacteraemia, considering the severity of the condition, that fosfomycin is active against the majority of the clinically relevant pathogens, like *S. aureus*, *E. coli*, *Klebsiella* spp. etc. and that it reaches high serum levels, and that the safety profile is acceptable, the CHMP concluded that the benefit-risk balance of fosfomycin IV in this indication is positive.

For the following indications the benefit-risk balance is considered negative by the CHMP:

- **Upper respiratory tract infections and Otitis media**

  The upper respiratory tract infections include different disease pattern involving the upper respiratory tract like bacterial sinusitis, pharyngitis, laryngitis or otitis media.

  No clinical data have been submitted that sufficiently establish efficacy of IV fosfomycin in indications of upper respiratory tract infections. Furthermore, these infections do not account for severe or life-threatening infections with limited treatment options are either self-limiting or well treatable with other antibiotics as recommended in the respective guidelines.

  Overall, taking the efficacy of IV fosfomycin and the characteristics of the conditions at stake (mild and/or self-limiting), the benefit-risk balance in the treatment of oto-, rhino-, laryngological infections is considered negative by the CHMP.

- **Ophthalmological infections**

  Ophthalmological infections like bacterial conjunctivitis are usually self-limiting diseases which are typically treated with topical antibiotics. Since these infections are considered as minor infections treatable with a wide range of topical antibiotics according to existing guidelines, the use of fosfomycin in these infections is considered inadequate.

  Only poor clinical evidence is available for the use of fosfomycin IV in the context of ophthalmological infections. The CHMP did not consider the efficacy sufficiently established in these indications.

  Overall, taking the available data of IV fosfomycin into consideration and the characteristics of the conditions at stake (mild and/or self-limiting), the benefit-risk balance in these indications is negative.

- **Peri-operative Infections**

  The term peri-operative/post-operative infection is considered to be medically unspecific. Post-operative infections are dependent on the type of surgical intervention, the key pathogens of the respective part of the body and can thus be different in characteristics. The efficacy is not established in this broad therapeutic indication. Therefore, the benefit-risk balance is considered negative.

- **Indications based on fosfomycin´s antibacterial activity and pharmacokinetic properties; Indications restricted to severe infections caused by microorganisms defined as susceptible in pharmacodynamics and Methicillin-resistant staphylococcal meningitis**

  Regarding these three indications, the CHMP considered that no specific indications were described, which would define the target disease within section 4.1. As such, this was considered a very unspecific description of the therapeutic indications and is not in accordance with the *SmPC Guideline* (Revision 2, 2009) nor the *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 rev 2).

  No clinical efficacy is demonstrated in this unspecific indication and therefore the CHMP concluded that the benefit-risk balance of IV fosfomycin in this indication is negative.

- **Severe infections of other organ systems due to fosfomycin-susceptible Gram-negative pathogens (see section 5.1) with limited therapeutic options**

This indication only covers the targeted therapy when susceptibility to IV fosfomycin has been confirmed prior to administration, and restricts its use to infections where the arsenal of eligible antimicrobial treatment options is intrinsically limited (e.g. due to reduced pharmacokinetic tissue accessibilities in severe infections of the eyes, ENT, prostate or bile duct with or without abscess formation). Although this might apply in isolated clinical situations with limited therapeutic options and represent a potential clinical need for IV fosfomycin, the CHMP concluded that this indication is too broad and only limited clinical data is available that are not sufficient to establish efficacy. Therefore, the benefit-risk balance in this indication is negative.

The CHMP also reviewed the dosage regimen for intravenous fosfomycin for the various approved indications and patient subpopulations. A dosing regimen of 12(16)-24 g/day is justified for all proposed indications in adult patients and adolescents over 12 years of age with normal renal function and mild-to-moderate renal impairment, taking into account that the individual dose must be selected dependent on the severity and site of infection, clinical situation of the patient (organ function, tolerability, comorbidities) and the susceptibility of the pathogen while confirming existing effective dosing regimens. The dosing recommendation in paediatric population was further reviewed based on PK modelling approaches and should be based on age and body weight. It should be noted that the PK modelling approaches (NAD/ PBPK model) used for PK modelling and simulation exhibit some limitations particularly with regard to variability. Thus, an optimisation of the PK models is recommended. This updated model should be considered for re-calculation of the PK/PD analyses for the paediatric population as soon as more clinical PK data are available (GARDP cooperation project).

New warnings were added to section 4.4 of the SmPC regarding the need for combination therapy to reduce the risk of selecting for resistance and also to highlight the need to monitor sodium and potassium levels due to a risk of sodium overload related with infusion of IV fosfomycin.

The CHMP also reviewed the existing data on adverse reactions observed with the use of intravenous fosfomycin. CHMP agreed that these risks can be minimised by appropriate warnings and recommendations in the product information. Finally, revisions were made to sections 5.1 and 5.2 to reflect current pharmacokinetic and pharmacodynamic data, including susceptibility testing breakpoints and prevalence of acquired resistance.

In conclusion, the CHMP is of the opinion that the benefit-risk balance of fosfomycin powder for solution for infusion remains positive, subject to the agreed changes to the product information as set out in Annex III to the opinion. The marketing authorisations should be varied accordingly.

Fosfomycin trometamol granules for oral solution (2g and 3g)

The benefit-risk balance of fosfomycin trometamol is considered positive in the following indications:

- **Uncomplicated cystitis in women and female adolescents**

The benefit-risk balance of fosfomycin trometamol is considered positive in the indication of uncomplicated cystitis in women and female adolescents. The available data shows that efficacy of fosfomycin is established in the treatment of cystitis in non-pregnant women. The short treatment with a single dose is associated with high compliance and the safety profile is acceptable. Due to the unique mechanism of action of fosfomycin, the risk of cross-resistances can be regarded as relatively low. In the view of available scientific data, the indication *treatment of uncomplicated urinary tract infections (acute cystitis) in women* is justified for fosfomycin single dose.

Regarding the appropriateness of a single dose of 3 g fosfomycin trometamol for the treatment of uncomplicated cystitis in premenopausal women, the totality of the available microbiological and clinical evidence based data from RCTs and meta-analysis currently indicates that a single 3g dose of

fosfomycin trometamol is the most adequate dose to treat acute uncomplicated UTIs in women and adolescents. Based on the data available, it is justified not to specify a lower weight limit of 50 kg in the product information for oral administered fosfomycin.

- **Perioperative antibiotic prophylaxis for transrectal prostate biopsy (TRPB) in adult man**

The CHMP concluded that there is insufficient evidence to establish the efficacy and safety of Fosfomycin in the broad indication "Periprocedural prophylaxis of urinary infections before surgical and transurethral diagnostic procedures" (please see below discussion on indications with negative benefit-risk balance for fosfomycin trometamol).

However, regarding the narrowed indication 'Perioperative antibiotic prophylaxis for transrectal prostate biopsy', CHMP considered that there is evidence to support a positive benefit-risk balance in this indication.

A variety of infectious complications may occur following TRPB, ranging from asymptomatic bacteriuria or UTI to prostatitis, sometimes with contingent bacteraemia and sepsis. Antimicrobial prophylaxis is recommended for patients undergoing TRPB, as it significantly reduces the incidence of these complications.

All available publications of clinical studies in different urological manoeuvres where fosfomycin was used were submitted and reviewed. In all studies fosfomycin trometamol demonstrated to be efficacious with a two-dose regimen in preventing infectious complications after these procedures. Three independently conducted meta-analyses were also reviewed which compared the efficacy of Fosfomycin trometamol with that of fluoroquinolones when used prophylactically for TRPB. All concluded that patients who received FT were less likely to develop infections.

Given the benefits of using chemoprophylaxis in urologic manoeuvres, the available clinical data, the prostatic penetration of fosfomycin, and a low prevalence of resistance in E. coli (most predominant causative pathogen of post-TRPB infections), fosfomycin is considered a valuable therapeutic alternative in perioperative antibiotic prophylaxis for transrectal prostate biopsy, especially in light of growing resistance to other agents, notably the fluoroquinolones conventionally used in TRPB.

The proposed dosing scheme with first dose administered 3 hours prior start of the procedure is well justified. However, the administration of the second dose 24 hours after the procedure was not thoroughly investigated in the submitted PK studies. Moreover, none of the submitted studies compared efficacy of one dose fosfomycin regimen with two doses regimen.

The two-dosing scheme, i.e. 3g sachet 3h prior to the procedure and one 3g sachet 24h after the procedure, as per the current approved dosage regimen remains acceptable. However, further evidence comparing the administration of one dose of fosfomycin regimen vs two doses regimen is required to confirm the current regimen.

In conclusion, the benefit-risk balance of the indication 'Perioperative antibiotic prophylaxis for transrectal prostate biopsy' is considered positive subject to the submission of further data to better characterise the suitability of the dosing scheme, specifically a phase I study in healthy volunteers including pharmacokinetic -pharmacodynamic analyses (please refer to annex IV of this Opinion). These pharmacokinetic -pharmacodynamic analyses should be conducted considering the "Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products" (EMA/CHMP/594085/2015).

Following indications of fosfomycin trometamol were concluded to have a negative benefit/risk balance:

- **Post-operative treatment of UTIs**
  No relevant data is available regarding the use of fosfomycin in postoperative infections. The publications discussed are all retrospective reviews of uncontrolled clinical trials or observational or cohort studies. They do not provide any evidence to justify the use of fosfomycin in postoperative urinary infections. No other relevant clinical data was submitted that would allow CHMP to conclude on a positive-benefit risk balance for the use of fosfomycin in post-operative treatment of UTIs. As such, the efficacy for this indication is not established and therefore the benefit-risk balance is negative.

- **Abundant asymptomatic bacteriuria**
  No data are available from published, controlled or uncontrolled clinical studies or from published reviews investigating the benefit of oral fosfomycin therapy and/or the potential risks of fosfomycin treatment in female patients with asymptomatic bacteriuria. Overall, taking into account the lack of efficacy data in this indication, the safety profile of fosfomycin and the disease condition the benefit-risk balance of oral fosfomycin therapy for the treatment of asymptomatic bacteriuria is considered negative.

- **Acute bacterial urethrovesical syndrome**
  No relevant data is available to support a positive benefit-risk balance for the use of fosofmycin in this indication. As such, the efficacy for this indication is not established and therefore the benefit-risk balance is negative.

- **Non-specific urethritis**

  Due to the lack of available data to support the use of Fosfomycin trometamol in non-specific urethritis and given the fact that the pathogen spectrum of non-gonococcal urethritis (NGU) is not sensitive to fosfomycin the CHMP concluded that the efficacy for this indication is not established and the benefit-risk balance is negative.

- **Recurrent UTIs**

  Based on the MAHs' responses, the long-term use (6-12 months) of fosfomycin in prevention of recurrent lower urinary tract infections is not considered substantiated. No convincing efficacy data or PK/PD data in support of this multiple-dose indication were identified. As such, the efficacy for this indication is not established and therefore the benefit-risk balance is negative.

- **Periprocedural prophylaxis (broad indication)**

  The overall view of the available scientific data indicates that there is insufficient evidence to support the broad indication "Periprocedural prophylaxis of urinary infections before surgical and transurethral diagnostic procedures" due to methodology limitations and different dosages used in the respective studies. Therefore, the efficacy for this indication is not established and the benefit/risk balance for the oral use of fosfomycin using multiple dosing regimens is negative.

- **Acute uncomplicated urinary tract infections in children**

  There is currently insufficient data from clinical trials conducted with acceptable methodological study quality available to justify the treatment of acute uncomplicated urinary tract infections in children aged 6 – 12 years with a single dose of 2 g fosfomycin trometamol. Moreover, the necessary assumptions for an extrapolation of the available data in adults to children are not fulfilled. As such, the efficacy for this indication is not established and the benefit-risk balance is negative.

- **Asymptomatic bacteriuria and acute cystitis during pregnancy**

  The evidence from clinical studies with regard to administration of oral fosfomycin in the sub-population of pregnant women are currently too limited, both concerning safety and efficacy, to establish a positive benefit risk balance which would justify a labelling in section 4.1. In addition, there is not sufficient evidence available to determine an appropriate treatment duration and dose. As such, the efficacy for this indication is not established and the benefit-risk balance is negative.

Due to substantial differences in section 4.3 of the different products, CHMP reviewed the current available date and harmonised the contraindications associated with the use of fosfomycin trometamol. The CHMP also reviewed the existing data on adverse reactions observed with the use of Fosfomycin trometamol. CHMP agreed that these risks can be minimised by appropriate warnings and recommendations in the product information. Finally, revisions were made to sections 5.1 and 5.2 to reflect current pharmacokinetic and pharmacodynamic data, including susceptibility testing breakpoints and prevalence of acquired resistance.

In conclusion, the CHMP is of the opinion that the benefit-risk balance of Fosfomycin trometamol 3 g granules for oral solution remains positive under normal conditions of use, taking into account the agreed changes to the product information as set out in Annex III to the opinion. The marketing authorisations should be varied accordingly.

CHMP also concluded that due to the deletion of the indication *Acute uncomplicated urinary tract infections in children* products containing fosfomycin 2g granules should be suspended subject to the conditions for lifting the suspension of the marketing authorisation as set out in Annex V of the opinion.

Fosfomycin calcium for oral use

Fosfomycin calcium is approved for the treatment of urinary tract infections, uncomplicated gastrointestinal infections and dermatological infections. According to the SmPC, the dose for all three indications in adults is 500 mg - 1 g every 8 hours (1-2 capsules or 2-4 tablespoons of 5 ml suspension every 8 hours).

Due to differences in the pharmacokinetic properties the extent of the existing data concerning safety and efficacy of fosfomycin trometamol that can be extrapolated to fosfomycin calcium is limited. The data on the recommended dose of fosfomycin trometamol are not applicable to fosfomycin calcium due to the different PK. Furthermore, data which justifies the labelled dosage recommendation for fosfomycin calcium (multiple dosages) is not available.

The submitted data concerning the urine concentration of fosfomycin calcium are extrapolated from data published for fosfomycin trometamol and need therefore to be interpreted with caution.

Regarding the submitted safety data it might be assumed that the safety profile of fosfomycin trometamol and fosfomycin calcium are similar, possibly with more gastrointestinal side effects due to poorer absorption of fosfomycin calcium.

For indications uncomplicated gastrointestinal infections and dermatological infections, no clinical data of fosfomycin calcium are available that have investigated the efficacy and safety and an appropriate dose regimen. Since fosfomycin trometamol is not approved for these indications, extrapolation of data of fosfomycin trometamol to fosfomycin calcium is not feasible. Altogether, it must be concluded that at present no data are available that would justify the use of fosfomycin calcium for the treatment of gastrointestinal and dermatological infection.

In view of the lack of efficacy and safety data for the indications treatment of gastrointestinal and dermatological infections the CHMP conclude that the benefit-risk balance of these indications are negative.

Regarding the indication 'Treatment of uncomplicated urinary tract infections (uUTI) in women' although limited data on the PK and efficacy of fosfomycin calcium are available the CHMP concluded that considering the available data and a positive safety profile of CaFO, there is sufficient evidence to establish a positive benefit-risk balance for this indication. However, due to the limitations of the available data the marketing authorisations for products containing fofomycin calcium for the treatment of uUTIs are subject to the submission of further data to better characterise the PK profile, including confirmation of the appropriate dose, and efficacy of fosfomycin calcium for the treatment of uUTI in adult women (please refer to annex IV of this Opinion).

The MAHs of fosfomycin calcium containing medicinal products shall commit:

- to provide results of the planned PK study and PK/PD/popPK analysis to national competent authority within 16 months after finalization of the referral procedure and before start of the non-inferiority trial,
- to provide the final study protocol for the non-inferiority trial in the indication uUTI in adult women to national competent authority within 18 months after finalization of the referral procedure taking the results of the PK-study and PK/PD/popPK analysis into account. The final study protocol should be submitted before start of the non-inferiority trial.

For fosfomycin trometamol the indication "acute uncomplicated urinary tract infection in children" was concluded with a negative risk-benefit balance since there were insufficient clinical evidence to support the use in children. Considering that no further data was provided for fosfomycin calcium in this population, the benefit-risk balance for the treatment of uUTIs in children with fosfomycin calcium is negative.

Fosfomycin for intramuscular use

This medicinal product is indicated for the treatment of infections of the genitourinary tract, respiratory tract and tissues caused by micro-organisms that are sensitive to fosfomycin (Fosfocina SmPC).

However, no relevant clinical data (including PK, efficacy and safety) were submitted to support this route of administration of fosfomycin during the referral and there is a lack of evidence regarding fosfomycin for intramuscular use. The available data for the intramuscular application of fosfomycin are very scarce and as such, the intramuscular application of fosfomycin is not satisfactorily supported by the published results up to date.

Considering all the above the benefit/risk balance of the intramuscular fosfomycin is considered negative. Therefore, CHMP recommends the suspension of fosfomycin products for intramuscular use subject to the conditions for lifting the suspension of the marketing authorisation as set out in Annex V of the opinion.

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 fosfomycin-containing medicinal products.
- The CHMP considered the totality of the data including the responses submitted by the marketing authorisation holders in writing and during an Oral Explanation, as well as the outcomes of a consultation with the Infectious Disease Working Party.

Fosfomycin powder for solution for infusion (intravenous fosfomycin)

- Taking into consideration the available clinical data and an acceptable safety profile the benefit-risk balance for fosfomycin powder for solution for infusion (intravenous fosfomycin) remains positive for the treatment of complicated urinary tract infections, infective endocarditis, bone and joint infections, hospital-acquired pneumonia including ventilator–associated pneumonia, complicated soft skin and tissue infections, bacterial meningitis, complicated intra-abdominal infections and bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections mentioned above when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment.
- The CHMP considered the available data to be sufficient to support revisions of the dosage regimen for intravenous fosfomycin for the various approved indications and patient subpopulations as well, as the need to harmonise the section on special warnings including the need to add new warnings for combination therapy and risk of sodium overload. The CHMP also reviewed the existing data on adverse reactions observed with the use of intravenous fosfomycin and concluded that these risks can be minimised by appropriate warnings and recommendations in the product information. It was also considered that the pharmacokinetic and pharmacodynamic data in the product information need to be updated as well.

Fosfomycin trometamol granules for oral solution (2g and 3g)

- Regarding fosfomycin trometamol 3 g granules for oral solution the CHMP considered that the benefit-risk balance remains positive in the treatment of acute uncomplicated cystitis in women and female adolescents. The CHMP also concluded on the appropriateness of a single dose of 3 g fosfomycin trometamol for this indication. There is currently insufficient data to establish a positive benefit-risk balance for the treatment of acute uncomplicated urinary tract infections in children aged 6 – 12 years with a single dose of 2 g fosfomycin trometamol. Therefore, the CHMP concluded that medicinal products containing fosfomycin 2 g granules should be suspended. To lift the suspension the MAH should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product in any indication.
- The CHMP concluded that the benefit-risk balance of the indication 'Perioperative antibiotic prophylaxis for transrectal prostate biopsy (TRPB) in adult men' is positive subject to a condition for the marketing authorisation holder(s) to further characterise the two-dose posology through generation of further evidence on the pharmacokinetic and pharmacodynamics of fosfomycin trometamol 3g with this dose regimen in this indication.
- The CHMP concluded on the harmonisation of contraindications associated with the use of fosfomycin trometamol. The CHMP also reviewed the existing data on adverse reactions observed with the use of fosfomycin trometamol granules for oral solution and concluded that these risks can be minimised by appropriate warnings and recommendations in the product information. It was also considered that the pharmacokinetic and pharmacodynamic data in the product information need to be updated as well.

Fosfomycin calcium for oral use

- Regarding fosfomycin calcium for oral use the CHMP concluded that in view of all the available data the efficacy and safety for the indications 'treatment of gastrointestinal and dermatological infections' has not been established and therefore that the benefit-risk balance of these indications is negative. Regarding the treatment of uncomplicated urinary tract infections in women the benefit-risk balance of this indication remains positive subject to a condition to the marketing authorisations to further characterise the pharmacokinetic profile

and to confirm the efficacy of fosfomycin calcium in the treatment of uncomplicated urinary tract infections in adult women.

Fosfomycin for intramuscular use

- In view of the insufficient data to establish the efficacy and safety, the CHMP concluded that the benefit-risk balance for intramuscular fosfomycin is negative and the medicinal products should be therefore suspended. To lift the suspension, the MAH should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product in any indication.

CHMP opinion

In view of the above, the Committee considers that the benefit-risk balance of fosfomycin powder for solution for infusion remains favourable subject to the agreed amendments to the product information.

In view of the above, the Committee also considers that the benefit-risk balance of fosfomycin 3 g granules for oral solution remains favourable subject to the agreed amendments to the product information and subject to a condition in the marketing authorisation. In order to further support the two-dose posology, in the indication 'Perioperative antibiotic prophylaxis for transrectal prostate biopsy', through generation of further evidence on the pharmacokinetic and pharmacodynamics of fosfomycin trometamol with this dose regimen in this indication, the MAH(s) should conduct and submit the results of a phase I study in healthy volunteers including pharmacokinetic - pharmacodynamic analyses.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for fosfomycin powder for solution for infusion and fosfomycin 3 g granules for oral solution.

Furthermore, in view of the above, the Committee considers that the benefit-risk balance of fosfomycin calcium for oral use remains favourable subject to a condition in the marketing authorisation for the indication treatment of uUTI in adult women. In order to further characterise the pharmacokinetic profile and efficacy of Fosfomycin calcium in the treatment of uncomplicated urinary tract infections in women the MAH(s) should conduct and submit the results of a pharmacokinetic study including population pharmacokinetic- and pharmacokinetic -pharmacodynamic analyses and a non-inferiority trial in the indication of uncomplicated urinary tract infections in adult women.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation of fosfomycin calcium for oral use.

In addition, the Committee, also considers that the benefit-risk balance of fosfomycin for intramuscular use and fosfomycin 2 g granules for oral solution use is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the suspension of the marketing authorisations for fosfomycin for intramuscular use and fosfomycin 2 g granules for oral solution use.

For the suspension of fosfomycin for intramuscular use to be lifted, the marketing authorisation holder(s) shall submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product in any indication.

For the suspension of fosfomycin 2g granules for oral solution containing medicinal products to be lifted, the MAH(s) should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product in any indication.