# Annex I

# List of nationally authorised medicinal products

# Annex IA

# List of nationally authorised medicinal products recommended for variation

**A. List of nationally authorised medicinal products recommended for variation**

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Austria | Sandoz Gmbh | Fosfomycin Sandoz | Fosfomycin Disodium 10.56g Vial | Powder For Solution For Infusion | Intravenous Use |
| Austria | Sandoz Gmbh | Fosfomycin Sandoz | Fosfomycin Disodium 5.28g Vial | Powder For Solution For Infusion | Intravenous Use |
| Austria | Sandoz Gmbh | Fosfomycin Sandoz | Fosfomycin Disodium 1.32g Vial | Powder For Solution For Injection | Intravenous Use |
| Croatia | Infectopharm Arzneimittel Und Consilium Gmbh | Fomicyt | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| Denmark | Infectopharm Arzneimittel Und Consilium Gmbh | Fosfomycin Infectopharm | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| Finland | Infectopharm Arzneimittel Und Consilium Gmbh | Fosfomycin Infectopharm | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| France | Panpharma | Fosfomycine Panpharma | Fosfomycin 1g Bottle | Powder For Solution For Injection | Intravenous Use |
| France | Panpharma | Fosfomycine Panpharma | Fosfomycin 1g Vial | Powder For Solution For Injection | Intravenous Use |
| France | Panpharma | Fosfomycine Panpharma | Fosfomycin 4g Bottle | Powder For Solution For Injection | Intravenous Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| France | Sanofi-Aventis France | Fosfocine Iv | Fosfomycin Sodium 1g Vial | Powder And Solvent For Solution For Injection | Intravenous Use |
| France | Sanofi-Aventis France | Fosfocine Iv | Fosfomycin Sodium 4g Vial | Powder And Solvent For Solution For Injection | Intravenous Use |
| Germany | Infectopharm Arzneimittel Und Consilium Gmbh | Fosfomycin Infectopharm | Fosfomycin Sodium 10.56g/10.76g | Powder For Solution For Infusion | Intravenous Use |
| Germany | Infectopharm Arzneimittel Und Consilium Gmbh | Infectofos | Fosfomycin Sodium 10.56g/10.76g | Powder For Solution For Infusion | Intravenous Use |
| Germany | Infectopharm Arzneimittel Und Consilium Gmbh | Infectofos | Fosfomycin Sodium 2.64g/2.69g | Powder For Solution For Infusion | Intravenous Use |
| Germany | Infectopharm Arzneimittel Und Consilium Gmbh | Infectofos | Fosfomycin Sodium 3.96g/4.04g | Powder For Solution For Infusion | Intravenous Use |
| Germany | Infectopharm Arzneimittel Und Consilium Gmbh | Infectofos | Fosfomycin Sodium 6.6g/6.73g | Powder For Solution For Infusion | Intravenous Use |
| Greece | Infectopharm Arzneimittel Und Consilium Gmbh | Fomicyt | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| Ireland | Infectopharm Arzneimittel Und Consilium Gmbh | Fomicyt | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| Italy | Infectopharm Arzneimittel Und Consilium Gmbh | Infectofos | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Netherlands | Infectopharm Arzneimittel Und Consilium Gmbh | Fomicyt | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| Norway | Infectopharm Arzneimittel Und Consilium Gmbh | Fosfomycin Infectopharm | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| Poland | Infectopharm Arzneimittel Und Consilium Gmbh | Infectofos | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| Spain | Laboratorios Ern, S.A. | Fosfocina Intravenosa | Fosfomycin Disodium 1g Vial | Powder And Solvent For Solution For Injection | Intravenous Use |
| Spain | Laboratorios Ern, S.A. | Fosfocina Intravenosa | Fosfomycin Disodium 4g Vial | Powder For Solution For Injection | Intravenous Use |
| Spain | Laboratorios Ern, S.A. | Fosfomicina Intravenosa Level | Fosfomycin 4g Vial | Powder For Solution For Injection | Intravenous Use |
| Sweden | Infectopharm Arzneimittel Und Consilium Gmbh | Fosfomycin Infectopharm | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| United Kingdom | Infectopharm Arzneimittel Und Consilium Gmbh | Fomicyt | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |
| United Kingdom | Infectopharm Arzneimittel Und Consilium Gmbh | Fosfomycin Infectopharm Arzneimittel Und Consilium | Fosfomycin 40mg/Ml | Powder For Solution For Infusion | Intravenous Use |

# Annex IB

# List of nationally authorised medicinal products recommended for variation and subject to conditions on the marketing authorisation

**B. List of nationally authorised medicinal products recommended for variation and subject to conditions on the marketing authorisation**

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Austria | Zambon S.P.A. | Monuril | Fosfomycin Trometamol 5.631g Bag | Granules For Oral Solution | Oral Use |
| Austria | Dr. Friedrich Eberth Arzneimittel Gmbh | Fosfomycin Eberth | Fosfomycin Trometamol 5.631g/8g | Granules For Oral Solution | Oral Use |
| Austria | Aristo Pharma Gmbh (Art 57) | Cystium | Fosfomycin Trometamol 5631mg Sachet | Powder For Oral Solution | Oral Use |
| Belgium | Zambon Nv | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Bulgaria | Zentiva, K.S. | Фосфомицин Зентива | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Bulgaria | Adipharm Ead | Фосфосептик | Fosfomycin Trometamol 5631mg Sachet | Granules For Oral Solution | Oral Use |
| Bulgaria | Zambon S.P.A. | Монурал | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Bulgaria | Zentiva, K.S. | Фосфомицин Зентива | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Croatia | Pharmas D.O.O. | Urifos | Fosfomycin 3g Sachet | Granules For Oral Solution | Oral Use |
| Croatia | Jadran-Galenski Laboratorij D.D. | Fosfomicin Jgl | Fosfomycin Trometamol 3g Bag | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Croatia | Sandoz D.O.O. | Urinex | Fosfomycin Trometamol 3mg Sachet | Granules For Oral Solution | Oral Use |
| Czech Republic | Exeltis Czech S.R.O. | Urifos | Fosfomycin Trometamol 5631mg Sachet | Granules For Oral Solution | Oral Use |
| Czech Republic | Apogepha Arzneimittel Gmbh | Rapidnorm | Fosfomycin Trometamol 5631mg Sachet | Granules For Oral Solution | Oral Use |
| Denmark | Zambon S.P.A. | Monurol | Fosfomycin 2g Units | Granules For Oral Solution | Oral Use |
| Denmark | Zambon S.P.A. | Monurol | Fosfomycin 3g Units | Granules For Oral Solution | Oral Use |
| Estonia | Zentiva, K.S. | Fosfomycin Zentiva | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Estonia | Zentiva, K.S. | Fosfomycin Zentiva | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Mylan S.A.S | Fosfomycine Adultes Mylan Pharma | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Ranbaxy Pharmacie Generiques | Fosfomycine Ranbaxy | Fosfomycin Trometamol 5631mg | Granules For Oral Solution In Sachet | Oral Use |
| France | Cristers | Fosfomycine Adultes Cristers | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Therabel Lucien Pharma S.A. | Uridoz | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution In Sachet | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| France | Laboratoires Urgo Healthcare | Fosfomycine Adultes Urgo | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Eg Labo Laboratoires Eurogenerics | Fosfomycine Eg | Fosfomycin 3g/8g | Granules For Oral Solution | Oral Use |
| France | Laboratoires Gerda | Fosfomycine Adultes Gerda | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Arrow Generiques | Fosfomycine Adultes Arrow | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Zentiva France | Fosfomycine Adultes Zentiva | Fosfomycin Trometamol 3g Sachet | Granules For Oral Solution | Oral Use |
| France | Nexmed Pharma | Fosfopharm | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| France | Evolupharm | Fosfomycine Adultes Evolugen | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Zambon France S.A. | Fostrofemge | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| France | Zambon France S.A. | Gynofostrome | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| France | Zambon France S.A. | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| France | Biogaran | Fosfomycine Biogaran | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| France | Sanofi-Aventis France | Fosfomycine Adultes Zentiva | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Teva Santé | Fosfomycine Adultes Teva Sante | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| France | Sandoz | Fosfomycine Sandoz | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| France | Laboratoires Neitum | Urofast Adultes | Fosfomycin Trometamol 5.631g Units | Oral Solution | Oral |
| Germany | Aliud Pharma Gmbh | Fosfomycin Al | Fosfomycin Trometamol 5.631g Dose | Granules For Oral Solution | Oral Use |
| Germany | Zambon Gmbh | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Germany | Uropharm Ag | Fosfomycin Uropharm | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Germany | Dr. Friedrich Eberth Arzneimittel Gmbh | Fosfomycin Eberth | Fosfomycin Trometamol 5.631g/8g | Granules For Oral Solution | Oral Use |
| Germany | Aristo Pharma Gmbh (Art 57) | Fosfomycin Aristo | Fosfomycin Trometamol 5631mg Bag | Powder For Oral Solution | Oral Use |
| Germany | Apogepha Arzneimittel Gmbh | Fosfuro | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Greece | Vocate Φαρμακευτικη Αε | Fosfocin | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Hungary | Exeltis Magyarország Kft. | Fosfomycin Exeltis | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Hungary | Zambon S.P.A. | Monural | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Ireland | Zambon S.P.A. | Monuril | Fosfomycin Trometamol 3g Units | Granules For Oral Solution | Oral Use |
| Italy | Mylan S.P.A. | Fosfomicina Adulti Mylan | Fosfomycin 3g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Ranbaxy Italia S.P.A. | Fosfomicina Adulti Ranbaxy | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Ranbaxy Italia S.P.A. | Fosfomicina Adulti Ranbaxy | Fosfomycin Trometamol 5.631g/Ml | Granules For Oral Solution | Oral Use |
| Italy | Ranbaxy Italia S.P.A. | Fosfomicina Bambini Ranbaxy | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Dymalife Pharmaceutical S.R.L. | Interfos Adulti | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Eg S.P.A. | Fosfomicina Eg | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Aurobindo Pharma (Italia) S.R.L. | Fosfomicina Adulti Aurobindo | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Zentiva Italia Srl | Fosfomicina Zentiva | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Italy | Zentiva Italia Srl | Fosfomicina Zentiva | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | S.F. Group Srl | Infeur Adulti | Fosfomycin 3g Bag | Granules For Oral Solution | Oral Use |
| Italy | Doc Generici S.R.L. | Fosfomicina Adulti Doc | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Zambon Italia S.R.L. | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Zambon Italia S.R.L. | Monuril Bambini | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Zambon Italia S.R.L. | Monuril Bambini | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Pensa Pharma S.P.A. | Fosfomicina Pensa | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | So.Se.Pharm S.R.L. | Berny | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Aristo Pharma Gmbh (Art 57) | Fosfomicina Adulti Aristo | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Aristo Pharma Gmbh (Art 57) | Fosfomicina Bambini Aristo | Fosfomycin Trometamol 3.754g | Granules For Oral Solution | Oral Use |
| Italy | Zentiva Italia Srl | Fosfomicina Zentiva | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Italy | Zentiva Italia Srl | Fosfomicina Zentiva | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Ratiopharm Gmbh | Fosfomicina Adulti Ratiopharm | Fosfomycin 3g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Sandoz S.P.A. | Fosfomicina Adulti Sandoz | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Italy | Sandoz S.P.A. | Fosfomicina Bambini Sandoz | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Italy | C&g Farmaceutici | Danifos Adulti | Fosfomycin Trometamol 5.631g Packet | Granules For Oral Solution | Oral Use |
| Lithuania | Zentiva, K.S. | Fosfomycin Zentiva | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Lithuania | Zentiva, K.S. | Fosfomycin Zentiva | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Luxembourg | Zambon Nv | Monuril | Fosfomycin Trometamol 5.631g | Granules For Oral Solution | Oral Use |
| Malta | Zambon S.P.A. | Monuril | Fosfomycin Trometamol 3g Units | Granules For Oral Solution | Oral Use |
| Netherlands | Zambon Nederland B.V. | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Poland | Exeltis Poland Sp. Z O.O. | Afastural | Fosfomycin Trometamol 3g Sachet | Granules For Oral Solution In Sachet | Oral |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Poland | Exeltis Poland Sp. Z O.O. | Afastural | Fosfomycin Trometamol 5631mg Sachet | Granules For Oral Solution | Oral Use |
| Poland | Symphar Sp. Z O.O. | Symural | Fosfomycin 3g Sachet | Granules For Oral Solution | Oral Use |
| Poland | Zambon S.P.A. | Monural | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Poland | Labiana Pharmaceuticals, S.L.U. | Uromaste | Fosfomycin 3g Sachet | Granules For Oral Solution | Oral Use |
| Portugal | Pharma Bavaria Internacional Portugal Unip. Lda | Fosmol | Fosfomycin Trometamol 5631mg Sachet | Granules For Oral Solution | Oral Use |
| Portugal | Pharmakern Portugal – Produtos Farmacêuticos, Sociedade Unipessoal, Lda. | Fosfomicina Pharmakern | Fosfomycin 3g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Portugal | Generis Farmacêutica, S.A. | Fosfomicina Generis | Fosfomycin 3000mg Sachet | Granules For Oral Solution | Oral Use |
| Portugal | Zambon - Produtos Farmacêuticos, Lda. | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Portugal | Zambon - Produtos Farmacêuticos, Lda. | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Portugal | Tolife - Produtos Farmacêuticos, S.A. | Fosfomicina Tolife | Fosfomycin Trometamol 3000mg Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Romania | Labiana Pharmaceuticals S.L.U. | Fosfomicina Labiana | Fosfomycin 3g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Romania | Zambon S.P.A. | Monural | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Slovakia | Exeltis Slovakia | Afastural | Fosfomycin Trometamol 3g Sachet | Granules For Oral Suspension In Sachet | Oral |
| Slovakia | Zambon S.P.A. | Monural | Fosfomycin 3g Units | Granules For Oral Solution | Oral Use |
| Slovakia | Dr. Friedrich Eberth Arzneimittel Gmbh | Fosfomycín Eberth | Fosfomycin Trometamol 5.631g/8g | Granules For Oral Solution | Oral Use |
| Spain | Kern Pharma, S.L. | Fosfomicina Kern Pharma | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Spain | Labiana Pharmaceuticals S.L.U. | Fosfomicina Labiana Pharma | Fosfomycin 3g Sachet | Granules For Oral Solution | Oral Use |
| Spain | Labiana Pharmaceuticals S.L.U. | Fosfomicina Labiana | Fosfomycin 3g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Spain | Laboratorios Q Pharma S.L. | Solufos | Fosfomycin Calcium 703mg Capsule | Capsule, Hard | Oral Use |
| Spain | Laboratorio Stada, S.L. | Fosfomicina Stada | Fosfomycin 3g/8g | Granules For Oral Solution | Oral Use |
| Spain | Farmalider, S.A. | Fosfomicina Farmalider | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Spain | Arafarma Group, S.A | Uroseptic | Fosfomycin Trometamol 5.631g Sachet | Powder For Oral Solution In Sachet | Oral Use |
| Spain | Zambon, S.A.U. | Monurol | Fosfomycin 3g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Spain | Qualigen, S.L. | Fosfomicina Qualigen | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Spain | Laboratorios Ern, S.A. | Fosfocina | Fosfomycin Calcium 500mg Capsule | Capsule, Hard | Oral Use |
| Spain | Laboratorios Ern, S.A. | Fosfocina | Fosfomycin Calcium 250mg/5ml | Powder For Oral Suspension | Oral Use |
| Spain | Abamed Pharma, S.L. | Fosfomicina Abamed Pharma | Fosfomycin 3g Sachet | Granules For Oral Solution | Oral Use |
| Spain | Abamed Pharma, S.L. | Fosfomicina Abamed | Fosfomycin 3g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Spain | Pensa Pharma, S.A.U. | Fosfomicina Pensa | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |
| Spain | Tarbis Farma, S.L. | Fosfomicina Tarbis | Fosfomycin Trometamol 3g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Sweden | Zambon S.p.A | Monurelle | Fosfomycin 3g Dose | Granules For Oral Solution | Oral Use |
| United Kingdom | Exeltis Poland Sp. Z O.O. | Fosfomycin Temapharm Sp. Z O.O. | Fosfomycin Trometamol 5631mg Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| United Kingdom | Mercury Pharmaceuticals Ltd. | Fosfomycin Mercury Pharmaceuticals | Fosfomycin Trometamol 5631mg Sachet | Granules For Oral Solution | Oral Use |
| United Kingdom | Zambon S.P.A. | Monuril | Fosfomycin Trometamol 5.631g Sachet | Granules For Oral Solution | Oral Use |

# Annex IC

# List of nationally authorised medicinal products recommended for suspension

**C. List of nationally authorised medicinal products recommended for suspension**

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Croatia | Pharmas D.O.O. | Urifos | Fosfomycin 2g Sachet | Granules For Oral Solution | Oral Use |
| Estonia | Zentiva, K.S. | Fosfomycin Zentiva | Fosfomycin 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Lithuania | Zentiva, K.S. | Fosfomycin Zentiva | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Lithuania | Zentiva, K.S. | Fosfomycin Zentiva | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Netherlands | Zambon Nederland B.V. | Monuril | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Poland | Labiana Pharmaceuticals, S.L.U. | Uromaste | Fosfomycin 2g Sachet | Granules For Oral Solution | Oral Use |
| Poland | Zambon S.P.A. | Monural | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Portugal | Pharmakern Portugal – Produtos Farmacêuticos, Sociedade Unipessoal, Lda. | Fosfomicina Pharmakern | Fosfomycin 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Portugal | Generis Farmacêutica, S.A. | Fosfomicina Generis | Fosfomycin 2000mg Sachet | Granules For Oral Solution | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Portugal | Zambon - Produtos Farmacêuticos, Lda. | Monuril | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Romania | Labiana Pharmaceuticals S.L.U. | Fosfomicina Labiana | Fosfomycin 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Romania | Zambon S.P.A. | Monural Pediatric | Fosfomycin Trometamol 3.754g Sachet | Granules For Oral Solution | Oral Use |
| Spain | Labiana Pharmaceuticals S.L.U. | Fosfomicina Labiana Pharma | Fosfomycin 2g Sachet | Granules For Oral Solution | Oral Use |
| Spain | Labiana Pharmaceuticals S.L.U. | Fosfomicina Labiana | Fosfomycin 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Spain | Arafarma Group, S.A | Uroseptic | Fosfomycin Trometamol 3.754g Sachet | Powder For Oral Solution In Sachet | Oral Use |
| Spain | Zambon, S.A.U. | Monurol | Fosfomycin 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Spain | Abamed Pharma, S.L. | Fosfomicina Abamed | Fosfomycin 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Spain | Abamed Pharma, S.L. | Fosfomicina Abamed Pharma | Fosfomycin 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |
| Spain | Tarbis Farma, S.L. | Fosfomicina Tarbis | Fosfomycin Trometamol 2g Sachet | Granules For Oral Solution In Sachet | Oral Use |

| Member State in EEA | Marketing authorisation holder | Product name | INN/Active substance + Strength | Pharmaceutical form | Route of Administration |
|---|---|---|---|---|---|
| Spain | Laboratorios Ern, S.A. | Fosfocina Intramuscuar | Fosfomycin Disodium 1g Vial, Lidocaine Hydrochloride 30mg Vial | Powder And Solvent For Solution For Injection | Intramuscular Use |
| Spain | Laboratorios Ern, S.A. | Fosfomicina Intramuscular Level | Fosfomycin 1g Vial | Powder And Solvent For Solution For Injection | Intramuscular Use |

# 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.

# Annex III

## Amendments to relevant sections of the Product Information

*Note:*

These amendments to the relevant sections of the Product Information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

**SUMMARY OF PRODUCT CHARACTERISTICS**

## Powder for solution for infusion

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*[This section should read as indicated below. Indications should only be implemented if the product was already approved for the condition]*

<Invented name> is indicated in all age groups for the treatment of the following infections when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment (see sections 4.2, 4.4 and 5.1):

- complicated urinary tract infections
- infective endocarditis
- bone and joint infections
- hospital-acquired pneumonia, including ventilator-associated pneumonia
- complicated skin and soft tissue infection
- bacterial meningitis
- complicated intra-abdominal infections
- bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

*[This section should read as follows:]*

Posology

The daily dose of fosfomycin is determined based on the indication, severity and site of the infection, susceptibility of the pathogen(s) to fosfomycin and the renal function. In children, it is also determined by age and body weight.

*[This section should read as indicated below. The table below should only include posology information of approved indications in line with section 4.1 above.]*

*Adults and adolescents (≥ 12 years of age) (≥ 40 kg):*

The general dosage guidelines for adults and adolescents with estimated creatinine clearance > 80 ml/min are as follows:

**Table 1 – dosing in adults and adolescents with CrCl >80 ml/min**

| **Indication** | **Daily dose** |
|---|---|
| Complicated urinary tract infection | 12–24 [a] g in 2–3 divided doses |
| Infective endocarditis | 12–24 g [a] in 2–3 divided doses |
| Bone and joint infections | 12–24 g [a] in 2–3 divided doses |

| | |
|---|---|
| Hospital-acquired pneumonia, including ventilator-associated pneumonia | 12–24 g [a] in 2–3 divided doses |
| Complicated skin and soft tissue infections | 12–24 g [a] in 2–3 divided doses |
| Bacterial meningitis | 16–24 g [a] in 3–4 divided doses |
| Complicated intra-abdominal infections | 12–24 g [a] in 2–3 divided doses |
| Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above | 12–24 g [a] in 2–3 divided doses |

Individual doses must not exceed 8 g.

[a] The high-dose regimen in 3 divided doses should be used in severe infections expected or known to be caused by less susceptible bacteria.

There are limited safety data in particular for doses in excess of 16 g/day. Special caution is advised when such doses are prescribed.

*[This section should read as follows:]*

*Duration of treatment*

Treatment duration should take into account the type of infection, the severity of the infection as well as the patient's clinical response.

*Elderly patients*

The recommended doses for adults should be used in elderly patients. Caution is advised when considering the use of doses at the higher end of the recommended range (see also recommendations on dosage for patients with impaired renal function).

*Renal impairment*

No dose adjustment is recommended in patients within estimated creatinine clearance between 40–80 ml/min. However, caution should be exercised in these cases, particularly if doses at the higher end of the recommended range are considered

In patients with impaired renal function the dose of fosfomycin must be adjusted to the degree of renal impairment.

Dose titration should be based on creatinine clearance values.

Table 2 shows the recommended dose adjustments for patients with a CrCL less than 40 mL/min:

**Table 2 – Dose adjustments for patients with a CrCL less than 40 mL/min**

| **$CL_{CR\ patient}$** | **$CL_{CR\ patient}/CL_{CR\ normal}$** | **Daily dosage recommended[a]** |
|---|---|---|
| 40 mL/min | 0.333 | 70% (in 2-3 divided doses) |
| 30 mL/min | 0.250 | 60% (in 2-3 divided doses) |
| 20 mL/min | 0.167 | 40% (in 2-3 divided doses) |
| 10 mL/min | 0.083 | 20% (in 1-2 divided doses) |

[a] The dose is expressed as a proportion of the dose that would have been considered appropriate if the patient's renal function were normal as calculated according to Cockgroft-Gault formula.

The first dose (loading dose) should be increased by 100%, but must not exceed 8 g.

*Patients undergoing renal replacement therapy*

Patients undergoing chronic intermittent dialysis (every 48 hours) should receive 2 g of fosfomycin at the end of each dialysis session.

During continuous veno-venous hemofiltration (post-dilution CVVHF), fosfomycin is effectively eliminated. Patients undergoing post-dilution CVVHF will not require any dose adjustment (see section 5.2).

*Hepatic impairment*

No dose adjustment is necessary in patients with hepatic impairment.

*Paediatric population*

Dose recommendations are based on very limited data.

Neonates, infants and children < 12 years of age (< 40 kg)

The dosage of fosfomycin in children should be based on age and body weight (BW):

**Table 13 – Dosing in children and neonates**

| **Age/weight** | **Daily dose** |
|---|---|
| Premature neonates (age [a] <40 weeks) | 100 mg/kg BW in 2 divided doses |
| Neonates (age [a] 40-44 weeks) | 200 mg/kg BW in 3 divided doses |
| Infants 1-12 months (up to 10 kg BW) | 200-300 [b] mg/kg BW in 3 divided doses |
| Infants and children aged 1≤12 years (10≤40 kg BW) | 200-400 [b] mg/kg BW in 3-4 divided doses |

[a] Sum of gestational and postnatal age

[b] The high-dose regimen may be considered for severe infections and or serious infections (such as meningitis), in particular when known or suspected to be caused by organisms with moderate susceptibility.

No dose recommendations can be made for children with renal impairment.

Method of administration

<Invented name> is intended for intravenous use.

The duration of infusion should be at least 15 minutes for the 2 g pack size, at least 30 minutes for the 3, 4 and 5 g pack size and at least 60 minutes for the 8 g pack size.

As damaging effects can result from inadvertent intra-arterial administration of products not specifically recommended for intra-arterial therapy, it is essential to ensure that fosfomycin is only administered into veins.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

**Section 4.3 Contraindications**

*[This section should read as follows:]*

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

**Section 4.4 Special warnings and precautions for use**

*[This section should read as follows:]*

Risk of selecting for resistance and the need for combination therapy

*In vitro*, fosfomycin has been found to rapidly select for resistant mutants. Also, the use of intravenous fosfomycin alone has been associated with selection of resistance in clinical studies. Whenever possible, it is recommended that fosfomycin is administered as part of a combination antibacterial drug regimen to reduce the risk of selecting for resistance.

Limitations of the clinical data

The clinical data to support the use of intravenous fosfomycin for treatment of some of the listed indications is limited by a lack of adequate randomised controlled trials. Furthermore, various dose regimens have been used and no single intravenous dose regimen has been strongly supported by clinical trial data. It is recommended that fosfomycin is selected to treat the listed indications only when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment (see sections 4.3 and 4.8). If such reactions occur, treatment with fosfomycin must be discontinued immediately and adequate emergency measures must be initiated.

*Clostridioides difficile*-associated diarrhea

*Clostridioides difficile*-associated colitis and pseudo-membranous colitis have been reported with fosfomycin and may range in severity from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of fosfomycin. Discontinuation of therapy with fosfomycin and the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sodium and potassium levels and risk of sodium overload

Sodium and potassium levels should be monitored regularly in patients receiving fosfomycin, in particular during prolonged treatment. Given the high content of sodium (0.32 grams) per gram of fosfomycin, the risk of hypernatraemia and fluid overload should be assessed before starting treatment, especially in patients with a history of congestive heart failure or underlying comorbidities such as nephrotic syndrome, liver cirrhosis, hypertension, hyperaldosteronism, pulmonary oedema or hypoalbuminemia as well as in neonates under sodium restriction. A low-sodium diet is recommended during treatment. An increase in the infusion length and/or a reduction to the individual dose (with more frequent administration) could also be considered. Fosfomycin may decrease potassium levels in serum or plasma, therefore potassium supplementation should be always considered.

Haematological reactions (including agranulocytosis)

In patients receiving fosfomycin intravenously haematological reactions including neutropenia or agranulocytosis have occured (see section 4.8). Therefore, the leukocyte count should be monitored at regular intervals and if such reactions occur, an adequate medical treatment should be initiated.

Renal impairment

In patients with impaired renal function, adjust the dosage according to the grade of renal insufficiency (see section 4.2).

Excipients

*[A warning about any excipient that would result in unwanted undesirable effects in patients with specific metabolism disorders (e.g. fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies (e.g against the colouring agent sunset yellow (E110)) should be added in this section. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]*

**Section 4.5 Interaction with other medicinal products and other forms of interaction**

*[This section should read as follows:]*

Specific concerns relating to INR imbalance:

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. The severity of the infection or inflammation, patient age and general state of health appear to be risk factors. Under these circumstances, it is difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly: fluoroquinolones, macrolides, cyclins, cotrimoxazole, and certain cephalosporins.

***Section 4.6 Fertility, pregnancy and lactation***

*[This section should read as follows:]*

Pregnancy:

There are no data from the use of intravenously administered fosfomycin in pregnant women. Fosfomycin crosses the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Fosfomycin should therefore not be prescribed to pregnant women unless the benefit outweighs the risk.

Breast-feeding:

After the administration of fosfomycin, low quantities were found in human milk. Only scarce information about fosfomycin use during breastfeeding is available, therefore this treatment is not recommended as first choice for a breastfeeding woman, especially if she is breastfeeding a premature or new-born baby. No specific risk for a breastfed child was demonstrated, however, as with any other antibiotics a potential risk of changes in infant bowel flora should be taken into consideration.

Fertility:

No data in humans are available. In male and female rats oral administration of fosfomycin up to 1000 mg/kg/day did not impair fertility (see section 5.3).

**Section 4.7 Effects on ability to drive and use machines**

*[This section should read as follows:]*

No specific studies have been performed but patients should be informed that confusion and asthenia have been reported. This may influence some patients' ability to drive and use machines (see section 4.8).

**Section 4.8 Undesirable effects**

*[This section should read as follows:]*

Summary of the safety profile

The most commonly reported adverse reactions during treatment are erythematous skin eruption, ion disbalances (see section 4.4), injection site reactions, dysgeusia and gastrointestinal disturbances. Other important adverse reactions include anaphylactic shock, antibiotic associated colitis and decreases in white blood cell counts (see section 4.4).

Tabulated list of adverse reactions

Undesirable effects are listed by body system and frequency using the following convention:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **System Organ Class** | **Frequency** | **Adverse reaction** |
|---|---|---|
| **Blood and lymphatic system disorders** | Not known | Agranulocytosis (transient), leucopenia, thrombocytopenia, neutropenia |
| **Immune system disorders** | Very rare | Anaphylactic reactions including anaphylactic shock and hypersensitivity (see section 4.4) |
| **Nervous system disorders** | Common | Dysgeusia, |
| | Uncommon | Headache |
| **Investigations** | Common | Hypernatremia, hypokalemia* (see section 4.4) |
| **Gastrointestinal disorders** | Uncommon | Nausea, vomiting, diarrhea |
| | Not known | Antibiotic-associated colitis (see section 4.4) |
| **Hepatobiliary disorders** | Uncommon | Blood alkaline phosphatase increased (transient), Transaminases increased (ALAT, ASAT), gamma-GT increased |
| | Not known | Hepatitis |
| **Skin and subcutaneous tissue disorders** | Common | Erythematous eruption |
| | Uncommon | Rash |
| | Not known | Angioedema, pruritus, urticaria |

| | | |
|---|---|---|
| **General disorders and administration site conditions** | Common | Injection site phlebitis |
| | Uncommon | Asthenia |

* see section below (Description of selected adverse reactions)

Description of selected adverse reactions:

Hypokalemia may result in diffuse symptoms such as weakness, tiredness or oedema and/or muscle twitching. Severe forms may cause hyporeflexia and cardiac arrhythmia. Hypernatremia may be associated with thirst, hypertension and signs of fluid overload such as oedema (see section 4.4). Severe forms may cause confusion, hyperreflexia, seizures and coma.

Paediatric population

Limited safety information is available from the paediatric population. Frequency, type and severity of adverse reactions may be expected to be similar to the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

***Section 4.9 Overdose***

*[This section should read as follows:]*

Experience regarding the overdose of fosfomycin is limited. Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin. In the event of overdose, the patient must be monitored (particularly for plasma/serum electrolyte levels), and treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

**Section 5.1 Pharmacodynamic properties**

*[This section should read as follows:]*

Pharmacotherapeutic group: Antibacterials for systemic use; Other antibacterials

ATC-Code: J01XX01

Mechanism of action

Fosfomycin exerts a bactericidal effect on proliferating pathogens by preventing the enzymatic synthesis of the bacterial cell wall. Fosfomycin inhibits the first stage of intracellular bacterial cell wall synthesis by blocking peptidoglycan synthesis.

Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3-phosphate and hexose-6 transport systems).

Pharmacokinetic/pharmacodynamic relationship

Limited data indicate that fosfomycin acts in a time-dependent manner.

Mechanism of resistance

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial fosfomycin transport systems. Further resistance mechanisms, which are plasmid- or transposon-borne, cause enzymatic inactivation of fosfomycin by binding the molecule to glutathione or by cleavage of the carbon-phosphorus-bond in the fosfomycin molecule, respectively.

Cross-resistance

Cross-resistance between fosfomycin and other antibiotic classes is not known.

Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing are as follows (EUCAST breakpoint table version 10):

| **Species** | **susceptible** | **resistant** |
|---|---|---|
| *Enterobacterales* | ≤ 32 mg/L | > 32 mg/L |
| *Staphylococcus* spp. | ≤ 32 mg/L | > 32 mg/L |

Susceptibility

The prevalence of acquired resistance of individual species may vary geographically and over time. Local information about the resistance situation is therefore necessary, particularly in order to ensure appropriate treatment of severe infections.

The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to fosfomycin or not.

**Commonly susceptible species**
***Aerobic Gram-positive microorganisms***
*Staphylococcus aureus*
***Aerobic Gram-negative microorganisms***
*Citrobacter freundii*
*Citrobacter koseri*
*Escherichia coli*
*Haemophilus influenzae*
*Neisseria meningitidis*
*Salmonella enterica*
***Anaerobic microorganisms***
*Fusobacterium* spp.
*Peptococcus* spp.
*Peptostreptococcus* spp.
**Species in which acquired resistance may be a problem**
***Aerobic Gram-positive microorganisms***
*Staphylococcus epidermidis*
*Streptococcus pneumoniae*
*Enterococcus* spp.
***Aerobic Gram-negative microorganisms***
*Enterobacter cloacae*
*Klebsiella aerogenes*
*Klebsiella oxytoca*
*Klebsiella pneumonia*

*Proteus mirabilis*
*Pseudomonas aeruginosa**
*Serratia marcescens*
***Anaerobic Gram-positive microorganisms***
*Clostridium* spp.
**Inherently resistant species**
***Aerobic Gram-positive microorganisms***
*Staphylococcus saprophyticus*
*Streptococcus pyogenes*
***Aerobic Gram-negative microorganisms***
*Legionella pneumophila*
*Morganella morganii*
*Stenotrophomonas maltophilia*
***Anaerobic Gram-negative microorganisms***
*Bacteroides* spp.
**Other mikroorganisms**
*Chlamydia* spp.
*Chlamydophila spp.*
*Mycoplasma* spp.

**Section 5.2 Pharmacokinetic properties**

*[This section should read as follows:]*

Pharmacokinetics

A single intravenous infusion of 4 g and 8 g of fosfomycin in young healthy males resulted in maximum serum concentrations ($C_{max}$) of approximately 200 and 400 µg/ml, respectively. The serum half-life was approximately 2 hours. In elderly and/or critically ill male and female subjects, single intravenous doses of 8 g of fosfomycin resulted in mean $C_{max}$ and half-lives in plasma of approximately 350–380 µg/ml and 3.6–3.8 h, respectively.

*Distribution*

The apparent volume of distribution of fosfomycin is approximately 0.30 l/kg body weight. Fosfomycin is distributed well to tissues. High concentrations are reached in eyes, bones, wound secretions, musculature, cutis, subcutis, lungs and bile. In patients with inflamed meninges, cerebrospinal fluid concentrations reach approximately 20–50% of the corresponding serum levels. Fosfomycin passes the placental barrier. Low quantities were found in human milk (about 8 % of the serum concentrations). The plasma protein binding is negligible.

*Metabolism*

Fosfomycin is not metabolised by the liver and does not undergo enterohepatic circulation. No accumulation is therefore to be expected in patients with hepatic impairment.

*Elimination*

80–90% of the quantity of fosfomycin administered to healthy adults is eliminated renally within 12 hours after a single intravenous administration. A small amount of the antibiotic is found in faeces (0.075%). Fosfomycin is not metabolised, i.e. the biologically active compound is eliminated. In patients with normal or mildly to moderately impaired renal function (creatinine clearance ≥ 40 ml/min), approximately 50–60% of the overall dose is excreted within the first 3-4 hours.

*Linearity*

Fosfomycin shows linear pharmacokinetic behaviour after intravenous infusion of therapeutically used doses.

*Special populations*

Very limited data are available in special populations.

*Elderly*

No dose adjustment is necessary based on age alone. However, renal function should be assessed and the dose should be reduced if there is evidence of renal impairment (see section 4.2).

*Paediatric population*

The pharmacokinetics of fosfomycin in children and adolescents aged 3–15 years as well as in term newborns with normal renal function are generally similar to those of healthy adult subjects. However, in renally healthy neonates and infants up to 12 months, the glomerular filtration rate is physiologically decreased compared to older children and adults. This is associated with a prolongation of the elimination half-life of fosfomycin in dependence on the stage of renal maturation.

*Renal insufficiency*

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency. Patients with creatinine clearance values of 40 ml/min or less require dose adjustments (see also section 4.2. "Renal impairment" for further details).

In a study investigating 12 patients under CVVHF customary polyethylene sulfone haemofilters with a membrane surface of 1.2 $m^2$ and a mean ultrafiltration rate of 25 ml/min were employed. In this clinical setting, the mean values of plasma clearance and elimination half-life in plasma were 100 ml/min, and 12h, respectively.

*Hepatic insufficiency*

There is no requirement for dosage adjustments in patients with hepatic insufficiency since the pharmacokinetics of fosfomycin remains unaffected in this patient group.

**Section 5.3 Preclinical safety data**

*[This section should read as follows:]*

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

No carcinogenicity data are available for Fosfomycin.

## Fosfomycin trometamol granules for oral solution (3g)

### 4.1 Therapeutic indications

*[This section should read as follows. Indications should only be implemented if the product was already approved for the condition]*

<Invented name> is indicated for (see section 5.1):

- the treatment of acute, uncomplicated cystitis in women and female adolescents

- perioperative antibiotic prophylaxis for transrectal prostate biopsy in adult man

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

*[This section should read as follows:]*

Posology

*Acute, uncomplicated cystitis in women and female adolescents (>12 years of age):* 3 g fosfomycin once

*Perioperative antibiotic prophylaxis for transrectal prostate biopsy:* 3 g fosfomycin 3 hours prior to the procedure and 3 g fosfomycin 24 hours after the procedure.

*Renal impairment:*

Use of <Invented name> is not recommended in patients with renal impairment (creatinin clearance < 10 ml/min, see section 5.2).

*Paediatric population*

The safety and efficacy of <Invented name>in children aged below 12 years of age have not been established.

Method of administration

For oral use.

For the indication of acute, uncomplicated cystitis in women and female adolescents it should be taken on an empty stomach (about 2-3 hours before or 2-3 hours after a meal), preferably before bedtime and after emptying the bladder.

The dose should be dissolved into a glass of water and taken immediately after its preparation.

### 4.3 Contraindications

*[This section should read as follows:]*

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### 4.4 Special warnings and precautions for use

*[This section should read as follows:]*

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment (see sections 4.3 and 4.8). If such reactions occur, treatment with fosfomycin must be discontinued immediately and adequate emergency measures must be initiated.

*Clostridioides difficile*-associated diarrhea

*Clostridioides difficile*-associated colitis and pseudo-membranous colitis have been reported with fosfomycin and may range in severity from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of fosfomycin. Discontinuation of therapy with fosfomycin and the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Paediatric population

The safety and efficacy of <Invented name> in children below 12 years of age have not been established. Therefore, this medicine should not be used in this age group (see section 4.2).

Persistent infections and male patients

In case of persistent infections, a thorough examination and a re-evaluation of the diagnosis is recommended as this is often due to complicated urinary tract infections or the prevalence of resistant pathogens (e.g. *Staphylococcus saprophyticus*, see section 5.1). In general, urinary tract infections in male patients have to be considered as complicated UTIs for which this medicinal product is not indicated (see section 4.1).

*Excipients*

*[A warning about any excipient that would result in unwanted undesirable effects in patients with specific metabolism disorders (e.g. fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies (e.g against the colouring agent sunset yellow (E110)) should be added in this section. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]*

**4.5 Interaction with other medicinal products and other forms of interaction**

*[This section should read as follows:]*

Metoclopramide:

Concomitant administration of metoclopramide has been shown to lower serum and urinary concentrations of fosfomycin and should be avoided.

Other medicinal products that increase gastrointestinal motility may produce similar effects.

Food effect:

Food may delay the absorption of fosfomycin, with consequent slight decrease in peak plasma levels and urinary concentrations. It is therefore preferable to take the medicinal product on an empty stomach or about 2 – 3 hours after meals.

Specific problems concerning the alteration in INR:

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. Risk factors include severe infection or inflammation, age and poor general health.

Under these circumstances, it is difficult to determinate whether the alteration in INR is due to the infectious disease or its treatment. However, certain classes of antibiotics are more often involved and in particular: fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

Paediatric population

Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation**

*[This section should read as follows:]*

Pregnancy:

Only limited data on the safety of fosfomycin treatment during 1st trimester of pregnancy (n=152) are available. These data do not raise any safety signal for teratogenicity so far. Fosfomycin crosses the placenta.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

<Invented name> should only be used during pregnancy, if clearly necessary.

Breast-feeding:

Fosfomycin is excreted in human milk in low quantities. If clearly necessary, a single dose of oral fosfomycin can be used during breast-feeding.

Fertility:

No data in humans are available. In male and female rats oral administration of fosfomycin up to 1000 mg/kg/d did not impair fertility.

**4.7 Effects on ability to drive and use machines**

*[This section should read as follows:]*

No specific studies have been performed but patients should be informed that dizziness has been reported. This may influence some patients' ability to drive and use machines (see section 4.8).

**4.8 Undesirable effects**

*[This section should read as follows:]*

Summary of the safety profile

The most common adverse reactions following the single-dose administration of fosfomycin trometamol involve the gastrointestinal tract, mainly diarrhoea. These events are usually self-limited in duration and resolve spontaneously.

Tabulated list of adverse reactions

The following table displays adverse reactions that have been reported with the use of fosfomycin trometamol from either clinical-trial or post-marketing experiences.

Undesirable effects are listed by body system and frequency using the following convention:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated form the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **System organ class** | **Adverse drug reactions** | | |
|---|---|---|---|
| | **Common** | **Uncommon** | **Not known** |
| Infections and infestations | Vulvovaginitis | | |
| Immune system disorders | | | Anaphylactic reactions including anaphylactic shock, hypersensitivity (see section 4.4) |
| Nervous system disorders | Headache, dizziness | | |
| Gastrointestinal disorders | Diarrhoea, nausea, dyspepsia, abdominal pain | Vomiting | Antibiotic-associated colitis (see section 4.4) |
| Skin and subcutaneous tissue disorders | | Rash, urticaria, pruritus | Angioedema |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**

*[This section should read as follows:]*

Experience regarding the overdose of oral fosfomycin is limited. Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin.

In the event of overdose, the patient must be monitored (particularly for plasma/serum electrolyte levels), and treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

**5.1 Pharmacodynamic properties**

*[This section should read as follows:]*

Pharmacotherapeutic group: Antibacterials for systemic use; Other antibacterials.

ATC code: J01XX01

Mechanism of action:

Fosfomycin exerts a bactericidal effect on proliferating pathogens by preventing the enzymatic synthesis of the bacterial cell wall. Fosfomycin inhibits the first stage of intracellular bacterial cell wall synthesis by blocking peptidoglycan synthesis.

Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3-phosphate and hexose-6 transport systems).

Pharmacokinetic/pharmacodynamic relationship

Limited data indicate that fosfomycin most likely acts in a time-dependent manner.

Mechanism of resistance

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial fosfomycin transport systems. Further resistance mechanisms, which are plasmid- or transposon-borne, cause enzymatic inactivation of fosfomycin by binding the molecule to glutathione or by cleavage of the carbon-phosphorus-bond in the fosfomycin molecule, respectively.

Cross-resistance

Cross-resistance between fosfomycin and other antibiotic classes is not known.

Susceptibility testing breakpoints

The susceptibility breakpoints established by the European Committee on Antimicrobial Susceptibility Testing are as follows (EUCAST breakpoint table version 10):

| **Species** | **susceptible** | **resistant** |
|---|---|---|
| *Enterobacterales* | ≤ 32 mg/L | > 32 mg/L |

Prevalence of acquired resistance

The prevalence of acquired resistance of individual species may vary geographically and over time. Local information about the resistance situation is therefore necessary, particularly in order to ensure appropriate treatment of severe infections.

The following table is based on data from surveillance programs and studies. It comprises organisms relevant for the approved indications:

**Commonly susceptible species**
***Aerobic Gram-negative microorganisms***
*Escherichia coli*
**Species in which acquired resistance may be a problem**
***Aerobic Gram-positive microorganisms***
*Enterococcus faecalis*
***Aerobic Gram-negative microorganisms***
*Klebsiella pneumonia*
*Proteus mirabilis*
**Inherently resistant species**
***Aerobic Gram-positive microorganisms***
*Staphylococcus saprophyticus*

**5.2 Pharmacokinetic properties**

*[This section should read as follows:]*

Absorption

After single-dose oral administration, fosfomycin trometamol has an absolute bioavailability of about 33-53%. Rate and extent of absorption are reduced by food, but the total amount of active substance excreted in the urine over time is the same. Mean urinary fosfomycin concentrations are maintained above an MIC threshold of 128 µg/mL for at least 24 h post 3 g oral dose in either the fasting or fed state, but the time to reach maximal concentrations in urine are delayed by 4 h. Fosfomycin trometamol undergoes enterohepatic recirculation.

Distribution

Fosfomycin does not appear to be metabolised. Fosfomycin is distributed to tissues including the kidneys and bladder wall. Fosfomycin is not bound to plasma proteins and crosses the placental barrier.

Elimination

Fosfomycin is excreted unchanged mainly via the kidneys by glomerular filtration (40-50% of the dose is found in the urine) with an elimination half-life of about 4 hours after oral use and to a lesser extent in faeces (18-28% of the dose). Even if food delays drug absorption, the total amount of drug excreted in the urine over time is the same.

Special populations

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency. Urinary concentrations of fosfomycin in patients with impaired renal function remain effective for 48 hours after a usual dose if creatinine clearance is above 10 ml/min.

In older people fosfomycin clearance is reduced in line with the age related reduction in renal function.

### *5.3 Preclinical safety data*

*[This section should read as follows:]*

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

No carcinogenicity data are available for Fosfomycin.

## Fosfomycin calcium for oral use

### 4.1 Therapeutic indications

*[This section should read as follows:]*

<Invented name> is indicated for treatment of uncomplicated urinary tract infections in women.

### 4.2 Posology and method of administration

*[Section 4.2 should only retain posology information pertinent for the use of Fosfomycin calcium in adults]*

**PACKAGE LEAFLET**

***Note: The existing package leaflet shall be amended to reflect the wording below.***

## Powder for solution for infusion

### 1. What <invented name> is and what it is used for

*[This section should read as indicated below. Indications should only be implemented if the product was already approved for the condition]*

<Invented name> contains the active substance fosfomycin. It belongs to a group of medicines called antibiotics. It works by killing certain types of germs (bacteria) that cause serious infectious diseases. Your doctor has decided to treat you with <Invented name> to help your body fight an infection. It is important that you receive effective treatment for this condition.

<Invented name> is used in adults, adolescents and children to treat bacterial infections of:

- the urinary tract
- the heart - sometimes called 'endocarditis'
- the bones and joints
- the lungs called "pneumonia"
- the skin and tissues below the skin
- the central nervous system
- the abdomen,
- the blood, when caused by any of the conditions listed above

### 2. What you need to know before you use <invented name>

*[This section should read as follows:]*

**Do not use <Invented name>:**

- if you are allergic to fosfomycin or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using <Invented name> if you suffer from one of the following disorders:

- heart problems (cardiac insufficiency), especially if digitalis medicine is taken (due to possible hypokalaemia)
- high blood pressure (hypertension)
- a certain disorder of the hormone system (hyperaldosteronism)
- high levels of blood sodium (hypernatraemia)
- fluid accumulation in the lungs (pulmonary oedema)

- kidney problems. Your doctor may need to change the dose of your medicine (see section 3 of this leaflet).
- previous episodes of diarrhea after taking or receiving any other antibiotics

**Conditions you need to look out for**

<Invented name> can cause serious side effects. These include allergic reactions, inflammation of the large intestine and a decreasing number of white blood cells. You must look out for certain symptoms while you are taking this medicine, to reduce the risk of any problems. See "Serious side effects" in Section 4.

**Other medicines and <Invented name>**

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

- anticoagulants, as their ability to prevent your blood from clotting might be altered by fosfomycin and other antibiotics.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.

Fosfomycin may pass to the baby in the womb or through breast milk. If you are pregnant or breast-feeding your doctor will only give you this medicine when it is clearly needed.

**Driving and using machines**

When <Invented name> is given, there may be side effects such as confusion and weakness. If these occur, you should not drive or operate machinery.

**3. How to use <Invented name>**

*[This section should read as follows:]*

<Invented name> is given to you into a vein (a drip) by a doctor or a nurse.

**Dosage**

The dose you will be given and the frequency of the dose will depend on:

- The type and severity of infection you have
- Your kidney function.

In children, it also depends on

- The child's weight
- The child's age

If you have problems with your kidneys or require dialysis, your doctor may need to reduce your dose of this medicine

<u>Route and method of administration</u>

For intravenous use.

<Invented name> is given to you into a vein (a drip) by a doctor or a nurse. The infusion will normally take 15 to 60 minutes, depending on your dose. Usually this medicine is given 2, 3 or 4 times a day.

**Duration of treatment**

Your doctor will decide how long your treatment should last depending on how fast your condition will improve. When treating bacterial infections it is important to complete the full course of treatment. Even after the fever has passed and the symptoms have abated, treatment should be continued for a few days more.

Certain infections, such as infections of the bones, may require an even longer treatment period after the symptoms have subsided.

**If you are given more <Invented name> than you should**

It is unlikely that your doctor or nurse will give you too much medicine. Ask them immediately if you think that you have been given too much of this medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

*[This section should read as follows:]*

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**

**Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:**

Signs of a serious allergic reaction (very rare: may affect up to 1 in 10,000 people,). These may include: breathing or swallowing problems, sudden wheezing, dizziness, swelling of eyelids, face, lips or tongue, rash or itching.

- Severe and persistent diarrhea, which may be associated with abdominal pain or fever (the frequency is unknown). This may be a sign of a serious bowel inflammation. Do not take medicines against diarrhea that inhibit the bowel movements (antiperistaltics).
- Yellowing of the skin or the whites of your eyes (jaundice, the frequency is unknown). This can be an early sign of liver problems.
- Confusion, muscle twitching or abnormal heart rhythm. This could be caused by high levels of blood sodium or low levels of blood potassium (common: may affect up to 1 in 10 people).

**Tell your doctor or nurse as soon as possible if you notice any of the following side effects:**

- Pain, burning, redness or swelling along the vein which is used during infusion of this medicine (common: may affect up to 1 in 10 people).
- You bleed or bruise more easily or get more infections than usual. This could be because you have a low number of white blood cells or blood platelets (the frequency is unknown).

**Other side effects can include:**

Common side effects (may affect up to 1 in 10 people)

- Taste disturbances

Uncommon side effects (may affect up to 1 in 100 people)

- Feeling sick, vomiting, or mild diarrhea

- Headache
- High levels of blood liver enzymes, possibly associated with liver problems.
- Rash
- Feebleness

Side effects with not known frequency (frequency cannot be estimated from the available data)

- Liver problems (hepatitis),
- Itching, hives

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## Fosfomycin trometamol granules for oral solution

**1. What <invented name> is and what it is used for**

*[This section should read as follows:]*

<Invented name> contains the active substance fosfomycin (as fosfomycin trometamol). It is an antibiotic that works by killing bacteria which can cause infections.

<Invented name> is used to treat uncomplicated infection of the bladder in women and female adolescents.

<Invented name> is used as antibiotic prophylaxis for transrectal prostate biopsy in adult man.

**2. What you need to know before you take <Invented name>**

*[This section should read as follows:]*

**Do not take <Invented name> if you:**

- are allergic to fosfomycin or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using <Invented name> if you suffer from one of the following disorders:

- persistent infections of the bladder,
- previously had diarrhea after taking any other antibiotics.

Conditions you need to look out for

<Invented name> can cause serious side effects. These include allergic reactions and an inflammation of the large intestine. You must look out for certain symptoms while you are taking this medicine, to reduce the risk of any problems. See "Serious side effects" in Section 4.

**Children and adolescents**

Do not give this medicine to children less than 12 years of age, as its safety and efficacy have not been established in this age group.

**Other medicines and <Invented name>**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

This is especially important if you are taking:

- **metoclopramide** or other medicinal products that increase the movement of food through the stomach and intestines, because they may reduce the uptake of fosfomycin by your body,
- **anticoagulants**, as their ability to prevent your blood from clotting might be altered by fosfomycin and other antibiotics.

**<Invented name> with food**

Food may delay the absorption of fosfomycin. Therefore, this medicinal product should be taken on an empty stomach (2-3 hours before or 2-3 hours after a meal).

**Pregnancy, breast-feeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant your doctor will only give you this medicine when it is clearly needed.

Breast-feeding mothers can take a single oral dose of this medicine.

**Driving and using machines**

You may experience side effects, such as dizziness, which may affect your ability to drive or use machines.

## 3. How to take <Invented name>

*[This section should read as follows:]*

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

In case of treatment of uncomplicated infection of the bladder, in women and female adolescents the recommended dose is 1 sachet of <Invented name> (3 g Fosfomycin).

When used as antibiotic prophylaxis for transrectal prostate biopsy the recommended dose is 1 sachet of <Invented name> (3 g fosfomycin) 3 hours prior to the procedure and 1 sachet of <Invented name> (3 g fosfomycin) 24 hours after the procedure.

Use in patients with renal impairment

This medicine should not be used in patients with severe renal impairment (creatinin clearance < 10 ml/min).

Use in children and adolescents

This medicine should not be used in children less than 12 years of age.

**Method of administration**

For oral use.

Take this medicine by mouth, on an empty stomach (2-3 hours before or 2-3 hours after a meal), preferably before going to bed after emptying the bladder.

Dissolve the content of one sachet in a glass of water and drink immediately.

**If you take more <Invented name> than you should**

If you accidentally take more than your prescribed dose, contact your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

*[This section should read as follows:]*

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**

**While taking <Invented name>, if you develop any of the following symptoms you should stop taking the medicine and contact your doctor immediately:**

- anaphylactic shock, a life threatening type of allergic reaction (the frequency is unknown). Symptoms include a sudden onset of rash, itching or hives on the skin and or shortness of breath, wheezing or difficulty in breathing,
- swelling of the face, lips, tongue or throat with breathing difficulties (angioedema) (the frequency is unknown),
- moderate to severe diarrhea, abdominal cramps, bloody stools and/or fever may mean that you have an infection of the large intestine (antibiotic-associated colitis) (the frequency is unknown). Do not take medicines against diarrhea that inhibit the bowel movements (antiperistaltics).

**Other side effects**

Common (may affect up to 1 in 10 people):

- headache
- dizziness
- diarrhea
- nausea
- indigestion
- abdominal pain
- infection of the female genital organs with symptoms like inflammation, irritation, itching (vulvovaginitis).

Uncommon (may affect up to 1 in 100 people):

- vomiting
- rash
- urticaria
- itching

Not known (frequency cannot be estimated from the available data):

- allergic reactions.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V.

By reporting side effects you can help provide more information on the safety of this medicine.

## Fosfomycin calcium for oral use

**1. What <invented name> is and what it is used for**

*[Information on indication should be updated as follows:]*

<Invented name> is used to treat uncomplicated infection of the bladder in women.

**3. How to take <Invented name>**

*[For Fosfomycin calcium capsules the information on posology should be updated as follows:]*

For the treatment of uncomplicated infection of the bladder, in women, the recommended dose is 500mg – 1g (1 or 2 capsules) every 8 hours.

*[For Fosfomycin calcium oral suspension the information on posology should be updated as follows:]*

For the treatment of uncomplicated infection of the bladder, in women, the recommended dose is 2 spoons of 5ml (500mg of Fosfomycin) or 4 spoons of 5ml (1g of Fosfomycin) every 8 hours.

# Annex IV

# Conditions to the marketing authorisations for Fosfomycin calcium and Fosfomycin trometamol medicinal products

**Conditions to the marketing authorisations**

The marketing authorisation holders for medicinal products containing Fosfomycin calcium shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

| | |
|---|---|
| In order 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 the MAH(s) should conduct and submit the results of: | |
| • A pharmacokinetic study including population pharmacokinetic and pharmacokinetic-pharmacodynamic analyses to further characterise the dosage regimen. | |
| The complete study protocols should be submitted to the relevant National Competent Authorities for agreement: | Within 1 month after Commission decision |
| The final study report should be submitted to the relevant National Competent Authorities: | Within 16 months after Commission decision |
| • A non-inferiority clinical trial to evaluate the efficacy in the indication of uncomplicated urinary tract infections in adult women. | |
| The complete study protocols should be submitted to the relevant National Competent Authorities for agreement: | Within 18 months after Commission decision |
| The final study report should be submitted to the relevant National Competent Authorities: | Within 30 months after Commission decision |

The marketing authorisation holders for medicinal products containing fosfomycin trometamol for the indication 'Perioperative antibiotic prophylaxis for transrectal prostate biopsy' shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

| | |
|---|---|
| In order to support the two-dose posology in the indication 'Perioperative antibiotic prophylaxis for transrectal prostate biopsy' the MAH(s) should conduct and submit the results of a phase I study in healthy volunteers including pharmacokinetic -pharmacodynamic analyses. | |
| The complete study protocols should be submitted to the relevant National Competent Authorities for agreement: | Within 1 month after Commission decision |
| The final study report should be submitted to the relevant National Competent Authorities: | Within 16 months after Commission decision |

# Annex V

# Conditions for lifting the suspension of the marketing authorisation(s) for Fosfomycin intramuscular and Fosfomycin trometamol (2g) medicinal products

## Conditions for lifting the suspension of the marketing authorisation(s)

Fosfomycin-containing medicinal products intended for intramuscular administration

For the suspensions of intramuscular fosfomycin containing medicinal products to be lifted, the competent authorities shall ensure that the below conditions have been completed by the marketing authorisation holders:

The MAHs should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product in any indication.

Fosfomycin trometamol 2g granules for oral solution

For the suspension of fosfomycin 2g granules for oral solution containing medicinal products to be lifted, the competent authorities shall ensure that the below conditions have been completed by the marketing authorisation holders:

The MAHs should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal product in any indication.