The silent flucytosine shortage in Europe – not a distant problem

Rosanne Sprute,[a,b,c] Seraina Duda,[d] Andrea Liekweg,[d] Michaela Simon,[e] and Oliver A. Cornely[a,b,c,f,*]

[a]Faculty of Medicine and University Hospital Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany
[b]Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), University of Cologne, Cologne, Germany
[c]German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany
[d]Hospital Pharmacy, University Hospital Cologne, Germany
[e]Institute for Medical Microbiology, Immunology, and Hygiene, University Hospital Cologne and Faculty of Medicine, University of Cologne, Cologne, Germany
[f]Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), University of Cologne, Cologne, Germany

The Lancet Regional Health - Europe 2023;30: 100658
Published Online xxx
https://doi.org/10.1016/j.lanepe.2023.100658

Flucytosine, originally developed as an anticancer agent in the 1950s and hence an old and off-patent drug, has become an irreplaceable treatment option for invasive fungal infections.

As the representative of one of four antifungal drug classes licensed in Europe, flucytosine is a central pillar in the treatment of cryptococcal infection. Its life-saving value is emphasized by recent high-quality randomized controlled trials evaluating flucytosine as a key component for cryptococcal meningitis treatment, most notably the ACTA trial published in 2018.[1] In addition, this antifungal has its role as combination partner in infections with difficult-to-treat pathogens such as resistant *Candida* spp. and rare fungi. These indications and its availability as both tablet and—in Europe—as intravenous (IV) formulation define the value of this drug in the treatment of invasive fungal infections. As a consequence, flucytosine has been listed as essential medicine by the WHO.

Despite this, access to flucytosine is not guaranteed in many African, South American, and Asian countries where cryptococcal meningitis is a frequent serious health threat. The shortage of flucytosine in these countries and associated constraints on patient care have been the subject of heated discussions.[2] The well-known availability problem has already been addressed years ago and the absence of drug registration and generic drug manufacturing impacting treatment costs have been identified as main barriers to access flucytosine in low- and middle-income countries (LMIC).[3]

There is an ongoing debate on alternate production methods, the costs of generic flucytosine, and registration costs in LMIC.[4] The relevance of flucytosine availability has led to continuous efforts of non-governmental organizations such as Médecins Sans Frontières (MSF) or Global Action For Fungal Infections (GAFFI) to improve access to this drug. In addition, several national access programs have been established to provide a minimum level of supply in LMIC.[5] Despite this public pressure, there has been no significant progress in availability and emotions on this topic are running high.[4]

What has not yet come to public attention is the fact that this supply shortage of flucytosine has also reached Europe.

The pharmaceutical company Mylan (now part of Viatris[6]) is currently the only company with a registered product and received WHO prequalification for flucytosine tablets in March 2018.[7] In early 2020, it was reported that Mylan had moved its manufacturing facility to India to reduce production costs of flucytosine.[4] In November 2020, Mylan informed about an inspection at the contract manufacturing site run by Legacy Pharmaceuticals Switzerland which uncovered a Good Manufacturing Practice (GMP) non-compliance event in relation to product sterility.[8] IV flucytosine has been produced exclusively by Legacy Pharmaceuticals Switzerland but this company does not exist any longer. As a result, intravenous flucytosine was listed as an active ingredient with "critical supply situation" by the German Federal Institute for Drugs and Medical Devices (BfArM).[9] So far, no new flucytosine IV-manufacturer has been approved although the marketing authorization of IV flucytosine is still valid in Germany.

Since then, the availability of flucytosine in Europe has been severely compromised. From a European viewpoint, neither production costs nor approval status are the major constraints, but the mere availability of the drug. Pharmacies in Europe have been working with remaining IV flucytosine stocks for two years. Flucytosine tablets are still available on some markets in the world, including France, Japan, and the United States, and may provide an alternative to IV solution in some patients. However, imported tablets can have several

*Corresponding author. Herderstrasse 52, 50931 Cologne, Germany.
E-mail address: oliver.cornely@uk-koeln.de (O.A. Cornely).

weeks delivery time and in various clinical situations IV administration is preferable, including critically ill patients and patients with reduced oral absorption. Resulting treatment difficulties and insufficiencies caused by the current flucytosine supply shortfall in Europe are not only alarming but unacceptable.

To address this plight, ingenious pharmacists and physicians have established access to flucytosine as compounded drug product for European hospitals.[10] However, this is only a temporary solution to a problem that has not yet been properly addressed by the authorities. Pharmaceutical companies need legal incentives or obligations to manufacture and distribute indispensable drugs such as flucytosine. When shortages occur despite these measures, administrative hurdles to import these products into the European market need to be reduced. For medical personnel, it seems abstruse that the production and distribution of a life-saving, off-patent drug is hampered by bureaucratic obstacles. Access to this essential drug for the treatment of deadly invasive fungal infections urgently needs to be improved in Europe and worldwide.

Contributors

RS wrote the original manuscript draft. SD, AL and MS critically revised the draft and contributed to manuscript writing. OAC conceived the idea, critically revised the draft and contributed to manuscript writing. All authors approved the final manuscript.

Declaration of interests

RS reports lecture honoraria and travel support from Pfizer, outside the submitted work. OAC reports grants and personal fees from Actelion, personal fees from Allecra Therapeutics, personal fees from Al-Jazeera Pharmaceuticals, grants and personal fees from Amplyx, grants and personal fees from Astellas, grants and personal fees from Basilea, personal fees from Biosys, grants and personal fees from Cidara, grants and personal fees from Da Volterra, personal fees from Entasis, grants and personal fees from F2G, grants and personal fees from Gilead, personal fees from Grupo Biotoscana, personal fees from IQVIA, grants from Janssen, personal fees from Matinas, grants from Medicines Company, grants and personal fees from MedPace, grants from Melinta Therapeutics, personal fees from Menarini, grants and personal fees from Merck/MSD, personal fees from Mylan, personal fees from Nabriva, personal fees from Noxxon, personal fees from Octapharma, personal fees from Paratek, grants and personal fees from Pfizer, personal fees from PSI, personal fees from Roche Diagnostics, grants and personal fees from Scynexis, personal fees from Shionogi, grants from DFG, German Research Foundation, grants from German Federal Ministry of Research and Education, grants from Immunic, outside the submitted work. SD has been working in the German Pharmacovigilance Department of Mylan until May 2017. AL and MS declare that they have no conflict of interest.

Acknowledgements

Funding: This comment was written as part of our routine work.

References

1 Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med*. 2018;378(11):1004–1017.
2 Temfack E, Lortholary O. Access to flucytosine for the treatment of HIV-associated cryptococcal meningitis in Africa. *Lancet Infect Dis*. 2022;22(9):1262–1264.
3 Loyse A, Thangaraj H, Easterbrook P, et al. Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries. *Lancet Infect Dis*. 2013;13(7):629–637.
4 https://corporateeurope.org/en/2020/06/unkept-promises-flucytosine. Accessed January 4, 2023.
5 Mashau RC, Meiring ST, Quan VC, et al. Outcomes of flucytosine-containing combination treatment for cryptococcal meningitis in a South African national access programme: a cross-sectional observational study. *Lancet Infect Dis*. 2022;22(9):1365–1373.
6 https://www.mylan.com/. Accessed January 4, 2023.
7 https://www.news24.com/health24/news/public-health/in-depth-what-the-approval-of-flucytosine-means-for-the-treatment-of-cryptococcal-meningitis-in-sa-20220420. Accessed January 4, 2023.
8 https://www.gov.uk/drug-device-alerts/class-2-medicines-recall-mylan-uk-healthcare-ltd-ancotil-2-5-g-250-ml-solution-for-infusion-pl-46302-0116-el-20-a-53. Accessed January 4, 2023.
9 https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/amInformationen/Lieferengpaesse/Liste_versorgungskritischer_wirkstoffe.pdf?__blob=publicationFile. Accessed January 4, 2023.
10 https://www.ecmm.info/wp-content/uploads/20220208_flucytosine-iv-availability.pdf. Accessed January 4, 2023.