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## Un thésaurus pour les indications hors AMM des antifongiques systémiques

### Thesaurus for off-label indications for systemic antifungal agents

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**Keywords:** antifungals, antifungal stewardship

## Résumé

**Objectifs.** Suite à la suppression des Protocoles Thérapeutiques Temporaires, un thésaurus des indications hors-AMM des antifongiques systémiques a été élaboré afin de réactualiser les pratiques cliniques et de maîtriser la prescription hors AMM.

**Matériel et méthodes.** Les dernières recommandations des sociétés savantes, ainsi que la bibliographie sur ce sujet, ont été analysées. Cette rédaction s'est faite dans le cadre d'une action de bon usage des antifongiques.

**Résultats.** Les libellés hors-AMM, les antifongiques concernés et les références par indication (prophylaxie, préemptif, empirique, curatif) ont été validés par le Groupe Antifongiques sous l'égide de la Commission du Médicament et des Dispositifs Médicaux Stériles et le Comité des Anti-Infectieux.

**Conclusion.** La complexification de la prise en charge des infections fongiques invasives nécessite que ce thésaurus soit partagé et utilisé comme un outil d'aide à la prise en charge des situations hors AMM.

## **Abstract**

**Objectives.** Following the removal of temporary treatment protocol procedures, we developed a thesaurus for off-label indications for systemic antifungals at our facility to update clinical practices and to control off-label prescriptions.

**Materials and methods.** Clinical practice guidelines and literature data were analyzed. This work was part of an antifungal stewardship program.

**Results.** Off-label wording (prophylaxis, preemptive, empirical, curative) and corresponding antifungals and references were validated by the multidisciplinary group for antifungal agents under the aegis of the Commission for the use of drugs and sterile medical devices and of the anti-infective committee.

**Conclusion.** Considering the complexity of invasive fungal infection management, this thesaurus needs to be shared and used as a helping tool to review off-label situations.

We developed a local thesaurus for off-label indications for systemic antifungal agents at a time when various reforms were being passed on the funding of health facilities [1,2] and when temporary treatment protocol procedures stopped being used.

The activity-based pricing system was implemented in France in 2004 alongside a specific funding plan for expensive drugs and medical devices as the amount related to the diagnosis-related group does not include the funding of such products [1]. Health facilities may charge expensive drugs, including a few antifungal agents, in addition to the fees related to the diagnosis-related group. This system ensures the fair management of all patients hospitalized in France.

Considering the high cost of these products, a three-party agreement for the proper use of drugs (French acronym CBU) was concluded in 2005 between our health facility, the Regional Health Agency (French acronym ARS), and the local sickness insurance fund to which the facility is affiliated [3]. Our facility therefore agreed to comply with the terms of the CBU for all additionally reimbursed products. Criteria for the proper use of drugs were defined by the French Agency for the Safety of Health Products (French acronym ANSM) as part of guidelines on drug stewardship published on its website. Reimbursement therefore applied to any indication included in the marketing authorization of the drug as well as to indications associated with a temporary treatment protocol procedure approved by the ANSM. The ANSM also defined unacceptable situations where no additional reimbursement is possible and situations requiring assessment for which reimbursement is possible provided both of the following conditions are met: the prescriber should justify the use of the drug using literature references and the justification should be documented in the patient's record.

In 2012 procedures called "temporary recommendations for use" (French acronym RTU) were implemented to replace temporary treatment protocol procedures [4]. Guidelines for the proper use of drugs associated with temporary treatment protocol procedures thus no longer applied. Since 2016 the reimbursement of additionally charged drugs is granted by indication and no longer by drug. Indications complying with the marketing authorization and reimbursable RTU still apply today. However, no RTU for antifungal agents has so far been granted. Off-label use based on rational clinical arguments and literature references may be reimbursed on a case-by-case basis. The Contract for improving the quality and

efficiency of care (French acronym CAQES) is replacing the CBU since 2018, but requirements for the proper use of drugs remain unchanged [5].

We decided to develop a thesaurus for off-label indications for systemic antifungal agents to compensate for the removal of temporary treatment protocol procedures and to control situations requiring off-label prescriptions. Off-label prescriptions account for 17% to 40% of prescriptions in our facility, depending on the wards. A 2014 assessment of antifungal prescriptions identified 18% of non-compliant prescriptions for aspergillosis and 11% for candidiasis. These non-compliant prescriptions were mainly due to the lack of prescribing guidelines in the facility (unpublished data). The development of the thesaurus was part of a much larger strategy for antifungal stewardship aiming at rationalizing the prescription of antifungal agents.

The thesaurus aims to fulfill the need for an update of clinical practices based on recent expert recommendations, but also the need for consideration of off-label prescriptions of antifungal agents. A more global objective is to ensure the fair management of all patients as acceptable off-label prescriptions are validated based on a consensus.

We developed the thesaurus following a close analysis of American (Infectious Diseases Society of America) and European guidelines (European Society of Clinical Microbiology and Infectious Diseases) to collect quality evidence levels for the various clinical situations. When recommendations were lacking, we looked for other specific scientific articles using the PubMed® database. Off-label prescriptions were also indexed based on the prospective monitoring of off-label indications performed by the pharmacies as part of the CBU. We also performed a comparative analysis of the marketing authorizations of antifungal agents listed in our facility to identify other off-label situations that would have otherwise be missed in clinical practice. The wording of the off-label situations was decided based on recent literature references, mainly expert recommendations, so as to be based on one or several literature references. The thesaurus was then submitted to and validated by the multidisciplinary group for antifungal agents under the aegis of the Commission for the use of drugs and sterile medical devices and of the Anti-infective committee.

Tables 1 to 3 detail the off-label wording, the antifungal agents concerned, the potential quality evidence levels defined by the Infectious Diseases Society of America, and the literature references by indication (prophylaxis, preemptive, empirical, curative).

## **Conclusion**

Antifungal prescription has become more complex over the past years: mycological diagnostic methods are more diverse, the number of available antifungal agents has increased, fungal diseases caused by rare or resistant fungi are more frequently observed, and patients requiring treatment are most often already taking several treatments and are highly immunodeficient. Tools for assisting antifungal prescription are therefore needed. This thesaurus thus fulfills this need as the most frequent off-label situations are listed in the thesaurus. These local guidelines could serve as the outline for developing national guidelines validated by scientific societies. The thesaurus is mainly aimed at prescribing physicians, most often infectious disease specialists who are frequently confronted with off-label prescriptions. Their access to literature references required to justify the prescription in the patient's record is therefore facilitated, especially as the justification is mandatory for off-label prescriptions to obtain reimbursement. The thesaurus is also aimed at hospital pharmacists so that they can have a tool to validate off-label prescriptions. The thesaurus thus acts as a guiding document offering an homogeneous ranking of off-label indications in hospital pharmacies and potentially enabling the identification of non-compliant clinical situations.

All facilities confronted with off-label prescriptions can use this thesaurus by adding their specific characteristics for antifungal prescriptions. The thesaurus is a prescribing tool that needs to be continuously updated. It will be adapted based on the referencing of new antifungal agents, the publication of new scientific articles, and the identification of new off-label clinical situations. The antifungal stewardship implemented in our facility contributed to the development and dissemination of the thesaurus and ensures its regular update.

**Acknowledgment**

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**Contribution of authors**

All authors contributed to writing the article and developing the thesaurus.

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We performed this work as part of our daily activities.

**Declaration of interests**

A.-L. B. was invited to conferences as speaker for MSD and as attendee for MSD and Gilead.

G. L. was invited to conferences as attendee and/or speaker for Mylan and Pfizer.

M. A. was invited to conferences as attendee for Gilead.



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- [5] Décret n° 2017-584 du 20 avril 2017 fixant les modalités d'application du contrat d'amélioration de la qualité et de l'efficience des soins <https://www.legifrance.gouv.fr/eli/decret/2017/4/20/AFSS1703616D/jo/texte> (accessed April 5, 2018)



**“Prophylaxis of invasive pulmonary aspergillosis in patients who underwent lung transplant or on a case-by-case basis in at-risk patients\*\*, mainly in construction sites”**

\*\*Refractory leukemia, solid tumors, solid organ transplants, corticosteroid treatment, COPD with progression of infiltrates despite antibiotic therapy, patients presenting with septic shock (Patterson TF, 2016)

Strong recommendation, moderate quality evidence

Weak recommendation, low quality evidence

Strong recommendation, moderate quality evidence

Weak recommendation, low quality evidence

Strong recommendation, moderate quality evidence

Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1-e60.

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Recommendations and quality evidence levels are from the Clinical Practice Guidelines of the Infectious Diseases Society of America (IDSA)

**Tableau 2.** Thésaurus hors AMM des antifongiques en préemptif et empirique

**Table 2.** Off-label thesaurus for preemptive and empirical antifungal therapies

Wording	Liposomal amphotericin B	Inhaled amphotericin B	caspofungin	fluconazole	itraconazole	micafungin	posaconazole	voriconazole	References
<p><b>“Preemptive treatment of invasive fungal infections in asymptomatic or febrile at-risk patients, with positive biomarker, especially in patients presenting with prolonged neutropenia (&gt;10 days) or in patients who underwent lung transplant”</b></p>	X		X						<p>Tan BH, Low JG, Chlebicka NL, Kurup A, Cheah FK, Lin RT, et al. Galactomannan-guided preemptive vs. empirical antifungals in the persistently febrile neutropenic patient: a prospective randomized study. <i>Int J Infect Dis</i> 2011;15:e350-6.</p> <p>Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. <i>Clin Infect Dis</i> 2009; 48:1042-51.</p> <p>Maertens J, Theunissen K, Verhoef G, Verschakelen J, Lagrou K, Verbeken E, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. <i>Clin Infect Dis</i> 2005;41:1242-50.</p>

<p><b>“Preemptive treatment of invasive candidiasis in asymptomatic or febrile at-risk patients*, with positive biomarker, especially in intensive care units or in case of solid organ transplant”</b>  <i>*Candida</i> colonization, disease severity, exposure to broad-spectrum antibiotics, major and recent surgery especially at the abdominal level, necrotizing pancreatitis, dialysis, parenteral nutrition, corticosteroids, presence of a central venous catheter (Pappas PG, 2016)</p>				<p>Strong recommendation, moderate quality evidence</p>					<p>Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1-50.</p>
<p><b>“Preemptive treatment of invasive pulmonary aspergillosis in asymptomatic or febrile at-risk patients**, with one positive biomarker but without any other microbiological documentation, especially in patients presenting with prolonged neutropenia (&gt;10 days) or in patients who underwent lung transplant”</b>  <i>**Refractory</i> leukemia, solid tumors, solid organ transplants, corticosteroid treatment, COPD with progression of infiltrates despite antibiotic therapy, patients presenting with septic shock (Patterson TF, 2016)</p>								<p>Strong recommendation, moderate quality evidence (prolonged neutropenia) Weak recommendation, moderate quality evidence (lung transplant)</p>	<p>Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1-e60.</p>

Recommendations and quality evidence levels are from the Clinical Practice Guidelines of the Infectious Diseases Society of America (IDSA)

**Table 2 (continued)**

**“Empirical treatment of invasive fungal infection in at-risk non-neutropenia septic patients, without any other microbiological documentation, especially in the intensive care unit or based on the infectious disease specialist’s opinion”**

Strong recommendation, low quality evidence

Strong recommendation, moderate quality evidence

Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1-e60.

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1-50.

**“Empirical treatment of invasive candidiasis in at-risk septic patients\*, without any other microbiological documentation, especially in the intensive care unit”**

\**Candida* colonization, disease severity, exposure to broad-spectrum antibiotics, major and recent surgery especially at the abdominal level, necrotizing pancreatitis, dialysis, parenteral nutrition, corticosteroids, presence of a central venous catheter (Pappas PG, 2016)

Strong recommendation,  
moderate quality evidence

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1-50.

Bassetti M, Marchetti M, Chakrabarti A, Colizza S, Garnacho-Montero J, Kett DH, et al. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of

**“Empirical treatment of patients presenting with a high suspicion of invasive pulmonary aspergillosis and at risk for sepsis\*\*, without any other microbiological documentation”**

\*\*Refractory leukemia, solid tumors, solid organ transplants, corticosteroid treatment, COPD with progression of infiltrates despite antibiotic therapy, patients presenting with septic shock (Patterson TF, 2016)

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Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1-e60.

Strong recommendation, moderate  
quality evidence

**Tableau 3.** Thésaurus hors AMM des antifongiques en traitement curatif

**Table 3.** Off-label thesaurus for curative antifungal therapies

Wording	Liposomal amphotericin B	Inhaled amphotericin B	caspofungin	fluconazole	isavuconazole	itraconazole	micafungin	posaconazole	voriconazole	References
<p><b>“Treatment of invasive fungal infections caused by a filamentous fungus or a yeast (rare or resistant or device infection) included in the spectrum of the molecule, as an alternative to other antifungal agents”</b></p>	X		X		X		X	X	X	<p>Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group.; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. Clin Microbiol Infect 2014;20 Suppl 3:76-98.</p> <p>Chowdhary A, Meis JF, Guarro J, de Hoog GS, Kathuria S, Arendrup MC, et al; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group.; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect 2014;20 Suppl 3:47-75.</p> <p>Tortorano AM, Richardson M, Roilides E, van Diepeningen A, Caira M, Munoz P, et al; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group.; European Confederation of Medical Mycology. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. Clin Microbiol Infect 2014;20 Suppl 3:27-46.</p>



