AESGP
VOICE OF EUROPEAN SELF-CARE INDUSTRY

AESGP Evidence Paper

Antifungals used in the self-care sector

February 2025

Introduction

AESGP supports the revision of the EU pharmaceutical law and the Commission's intention to modernize the EU pharmaceuticals regulatory environment. AESGP is, however, concerned that some **provisions could result in unintended consequences such as the restriction of access to commonly used non-prescription medicines. For example, the proposal to restrict access to common antifungal and antiviral non-prescription medicines by making them subject to prescription.**

While supporting the European Action Plan against Antimicrobial Resistance and the objectives of the Chemical Strategy for Sustainability, AESGP believes that the **prescription status of antimicrobial products (in particular, antifungals and antivirals) should be restricted to those products for which an AMR risk has been confirmed as a public health threat.**

This proposal would make all antifungal and antiviral medications that are currently available over the counter to treat minor conditions like athletes' foot, lip herpes (cold sores), skin warts, dandruff, vaginal thrush, minor eye infections in otherwise healthy citizens only available via prescription from a doctor.

Making treatments for these infections prescription-only will negatively impact European citizens and have significant impact on healthcare systems. Instead of getting advice and access to treatments in their local pharmacy, citizens would have to visit a Family Doctor or a General Practitioner for a prescription. This would increase health care costs and add pressure to already-stretched health systems and would ultimately impact how quickly such simple conditions can be treated. Delaying treatment could increase severity and transmission of these infections further exacerbating the situation.

We consider that this proposal is a disproportionate and unnecessary risk mitigation since there is no evidence to suggest that self-care usage of antifungal or antiviral medicinal products give rise to antimicrobial resistance.

- The risks of resistance are linked with specific underlying conditions (e.g., immunocompromised patients) for which antivirals and antifungals are prescribed at high doses and via systemic routes. The risk of resistance in these populations is accrued if the antifungal/antivirals are used inappropriately, especially during long course of systemic treatments.

- Non-prescription antiviral and antifungals have well defined indicated usages and are generally used in lower doses and via topical routes of administration. There is no evidence that non-prescription medicines are associated with AMR.

- The proposal to restrict all antifungals and antimicrobials to prescription legal status would not answer the current problem of AMR. Instead, it would deprive people suffering from self-limiting conditions from fast access to efficacious treatments. It would drive an unnecessary need of doctors' resources whilst adding cost to already stretched national health funds. Furthermore, a fast onset of treatment is mandatory for those minor conditions not to spread or aggravate (e.g., *tinea inguinalis* can spread to the genital area) resulting in worsened clinical outcomes.

- A case-by-case decision on prescription status taken by regulatory authorities on each medicinal product at time of marketing authorization approval is a more appropriate and proportionate approach.

Summary

Cases of invasive fungal disease are rising. This rise is directly linked to the rise in the number of immunocompromised people as a result of changes in medical practice, such as the use of powerful immunosuppressive medications and intense chemotherapy (WHO 2022, Hossain et al. 2022, Mc Dermott 2022).

At the present time, resistance to antifungals is still low for most common pathogens. The initial concern that the frequent use of OTC antifungals for local/ topical therapy may promote the development of resistance with cross-resistance to systemically applied antifungals (Cross et al. 2000) appears largely unfounded. After decades of use, it can be claimed that upon use of OTC antifungals in the approved indications and according to the product information, the prescription-free use can be considered safe for humans, as exemplified by clotrimazole. Despite its use over decades, clotrimazole resistance is rare in the general population, with the caveat that drug resistance has emerged in immunocompromised patients. The development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions (EDQM 2017). Susceptibility testing is usually not recommended for clotrimazole (Mendling et al. 2020). The same applies to bifonazole, a widely used topical antifungal. Despite its use over many years, the resistance situation for bifonazole is favourable.

The risk of resistance development to antifungals exists if the antifungals are used inappropriately, especially during long courses of systemic treatment with persistently low drug concentrations in the systemic circulation and tissues (Perlin et al. 2017, Fisher et al. 2022, Carmo et al. 2023). In fact, one of the best methods to avoid acquiring resistance is to take antifungal medication as directed (Hossain et al. 2022).

Antifungal prophylaxis under the care of healthcare professionals can reduce morbidity and mortality from invasive fungal disease. Its use needs to be optimised and appropriately targeted to patients at highest risk to derive the most benefit (Teh et al. 2021). This is of particular importance in special populations (children, multi-morbid patients) where absorption, distribution, metabolism and clearance of antifungal medications can be affected (Ramos et al. 2019). These patients will have to go continuous medical supervision.

The reason for this is that the immunological condition of the host is crucial since antifungal medicinal products must cooperate with the immune system to control and eradicate an infection. Antifungal therapy is more likely to fail in patients with considerable immunological dysfunction since the medication must fight the infection on its own without the assistance of the immune system (Hossain et al. 2022).

The heterogenous group of immunocompromised patients which makes up about 2–3% of the overall population, includes people with human immunodeficiency virus (HIV) infection, cancers, transplants, primary immunodeficiencies and those treated with immunosuppressive biologics and medications. Their underlying etiologies and demographics contribute to multifactorial and interrelated causes for immune compromise.

In addition to impaired responses to infection, immunocompromised patients tend to be older, have additional comorbid conditions beyond immunosuppression, and have fewer reserves to recover from the physiological challenges of acute infection. (Shoham et al 2023). Taken this into account, these patients are under continuous medical treatment and supervision anyway, because of their underlying health condition and will therefore, always consult their medical attending physician before taking any medication whether available upon prescription or not.

Existing non-prescription antifungal treatments available to the general population have restricted indications, limited to mild or moderate localized (ringworm, thrush) fungal infections and for well-established and self-identifiable diseases. They are not indicated in any case to treat complicated or invasive fungal infections in any of its forms (Antifungal Antibiotics - StatPearls - NCBI Bookshelf (nih.gov).

Antifungal resistance can also be acquired by other factors (e.g. improper drug disposal, poor patient compliance, when doses are skipped, therapy is stopped too soon, or the dose is too low) (Pai et al. 2018, Hossain et al. 2022, Gupta and Venkataraman 2022, Baid 2022).

The European Union at the same time is helping developing strategies to protect human, environmental and animal health with programmes such as EU4Health programme, where within its objectives, aims at not only

improving the availability, accessibility and affordability of medicinal products and medical devices, but also by fostering healthy lifestyles and promoting access to healthcare with specific programmes and proposed measures aiming at the above (Regulation (EU) 2021/522 of the European parliament and of the council of 24 March 2021).

Switching non-prescription antifungal drugs back to prescription drugs would not only burden the health care system to an unpredictable extent, it would also prevent patients from having full and reliable access to health care resources in the presence of minor conditions they can take care of themselves.

Nowadays, the importance of self-care/"health care in your own hands", health literacy, knowledgeable patient/consumer, lifting burden on healthcare systems, etc. is emphasized by various parties and national health funds. Switching back to compulsory prescription would achieve exactly the opposite with feeling patients to have been disempowered to take care of themselves - superfluously, since the risk of resistance development is evidently low for non-prescription antifungals.

Risk reduction strategies aimed at minimizing the emergence of resistance to OTC antifungals may include several approaches. For Portugal, the second biggest consumer of OTC antifungals in Europe, a research group from Porto recommended to engage physicians and pharmacists to provide educational information to the general public about antifungal drugs consumption. Pharmacists and other pharmacy staff should receive continuing education about how to control the spread of infections and antimicrobial resistance. This would improve their counselling of patients exhibiting characteristic signs and symptoms of fungal infections. With regard to general stores and supermarkets, it was proposed to implement measures to improve staff knowledge (e.g. interactive educational workshops for the workers involved) (Manuel da S Azevedo et al. 2016).

Also, outside Portugal, educational programs could limit antifungal medication misuse and improve patient compliance. Specifically, consumers must be careful about how they dispose drugs and that they have to follow correct dosing regimens. Most importantly, they should ensure to take the entire regimen of antifungals to ensure complete eradication? of the pathogen and to prevent the rise of resistance (Perlin et al. 2017, Baid 2022).

Generally, because invasive fungal diseases are most common in immunocompromised patients, host-directed approaches are needed to lessen the pressure on antifungal drugs (Fisher et al. 2022, Rabaan et al. 2023).

Methods and search strategy

Systematic database searches for relevant, publicly available literature were performed using the ProQuest Dialog DataStar service; several combinations of key words were applied. The databases that were searched included Medline®, Embase® and Biosis®. In addition, references cited in related publications were followed up. The Internet was also screened for relevant information. The literature searches covered the period from 1990 to June 2023 (lock date: June 20, 2023).

Primary resistance, or intrinsic resistance, is a term used to describe fungal species in which an innate resistance to an antifungal exists, without prior exposure to the drug. Secondary resistance, or acquired resistance, refers to the development of resistance in a previously susceptible fungal species in response to drug pressure.

Is there a risk of resistance with clinical consequences in humans posed by molecules and dosage forms available in self-care?

Clotrimazole

Clotrimazole is an imidazole antimycotic agent that was discovered in the 1960s. Clotrimazole has a broad antimicrobial activity against *Candida albicans* and other fungal species. Like other azole-type antifungal drugs, the antimycotic properties are mediated by an interaction with ergosterol synthesis (via inhibition of the fungal cytochrome 14α-demethylase enzyme) eventually resulting in increased fungal cell wall leakiness with disruption of the structure and function of the cell wall. Topical clotrimazole is widely used for the treatment of *tinea pedis* (athlete's foot), cutaneous mycoses and oropharyngeal candidiasis. It also belongs to the drugs of choice for the topical treatment of vulvovaginal candidiasis and *Candida balanitis* (Workowski et al. 2021, Wray et al. 2022). Clotrimazole was first registered as Canesten® in Germany in 1973. It has only been used in topical formulations (e.g. cream, ointment, solution) (Carmo et al. 2023). The initial formulation for local treatment of vulvovaginal candidiasis was the vaginal tablet followed by internal vaginal cream, external cream and soft ovule. Additional topical formulations are marketed under other trade names. Drug combinations (e.g. clotrimazole plus fluconazole) are also available nowadays. Clotrimazole monopreparations are available over the counter in most countries (Mendling et al. 2020).

Primary and secondary resistance to clotrimazole

Primary resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions (EDQM 2017). Susceptibility testing is usually not recommended (Mukasa et al. 2015, Mendling et al. 2020).

Despite its use over many years, clotrimazole resistance is rare, with the caveat that drug resistance has emerged particularly in immunocompromised patients. Resistance has been associated with the overexpression of efflux pump genes. Changes in the clotrimazole target, the fungal cytochrome 14α-demethylase enzyme, may also play a role in some cases (Crowley and Gallagher 2014, Mendling et al. 2020).

Bifonazole

Bifonazole is an imidazole antimycotic agent that is in clinical use for decades. It has a broad antimycotic action spectrum, which includes dermatophytes, yeasts, moulds and other fungi (Bari 2013, Czaika et al. 2014). Bifonazole has increased fungicidal activity on filamentous fungal elements, in particular of dermatophytes, owing to a twofold inhibition of ergosterol biosynthesis in fungal cells. Bifonazole acts more strongly against filamentous fungi and fungal elements; this is important in *Candida* species infection as the parasitic, invasive mycelia are most sensitive to bifonazole (Bayer 2016, SmPC 2023). In fact, bifonazole exerts its antifungal action by inhibiting the biosynthesis of ergosterol on two different levels, thereby distinguishing bifonazole both from most other azole derivatives and from other antifungals which act on a single level (SmPC 2023). It has been used in creams, gels, solutions and powders (in a strength of ≤ 1%), applied once a day to treat superficial fungal infections of the skin, such as dermatophytoses, cutaneous candidiasis and pityriasis versicolor. Topical bifonazole preparations are available over the counter.

Primary and secondary resistance to bifonazole

Despite its use over many years, the resistance situation for bifonazole is favourable. Primary resistant variants of sensitive fungal species are very rare. Investigations so far did not provide any evidence of a development of secondary resistance in primarily sensitive strains (SmPC 2023).

Bifonazole is frequently used as reference drug in the evaluation of new antifungal drugs (e.g. Zveaghintseva et al. 2021, Petrou et al. 2023). It appears to be also effective against *Candida auris*, a multidrug-resistant yeast-like fungus (Ito et al. 2023).

Fluconazole

Fluconazole is a triazole antimycotic agent that is in clinical use since the 1980s. It is one of the most widely used antifungal agents. Fluconazole's spectrum of activity includes most *Candida* species, *Cryptococcus neoformans*, some dimorphic fungi and dermatophytes, among others (Bayer 2019).

Fluconazole is commonly used to treat infections caused by *Candida* species, including oral candidiasis, vulvovaginal candidiasis and systemic fungal infections such as cryptococcal meningitis and invasive candidiasis. It may also be used to prevent fungal infections in immunocompromised individuals, such as those with HIV/AIDS or undergoing chemotherapy (Govindarajan et al. 2023). These patients are under close medical supervision and align on other treatments with their physicians. L

ike other azole-type antifungal drugs, the antimycotic properties are mediated by an interaction with ergosterol synthesis (via inhibition of the fungal cytochrome 14α-demethylase enzyme) eventually resulting in increased fungal cell wall leakiness with disruption of the structure and function of the cell wall. Fluconazole is available as oral and intravenous formulations. In some countries, oral 150 mg single dose preparations are available over the counter.

Primary and secondary resistance to fluconazole

Fluconazole resistance can occur in certain fungal species, but the incidence of resistance varies depending on the geographic region, the specific fungal species involved, and the patient population being studied. In general, the overall prevalence of fluconazole resistance is relatively low. Specifically, in the USA and Europe, the incidence of fluconazole resistance for *Candida albicans*, *Candida tropicalis* and *Candida parapsilosis* is low, at approximately 2%, 5% and 4%, respectively; similar rates of fluconazole resistance are observed in Asia-Pacific and India. *Candida krusei* is considered intrinsically resistant to fluconazole (Castanheira et al. 2017, Berkow et al. 2020). The resistance is driven by prescription usage and linked to the conditions of patients (e.g., immunocompromised patients).

The incidence of fluconazole resistance has been reported to be higher in specific patient populations, such as those with recurrent or long-term exposure to fluconazole, or patients with a compromised immune system (Berkow and Lockhart 2017).

Resistance has been associated with the overexpression of efflux pump genes, change in the fluconazole target, ergosterol biosynthesis pathway alteration, increased drug metabolism and enhanced DNA repair mechanisms (Berkow and Lockhart 2017, Berkow et al. 2020).

Miconazole

Miconazole is an imidazole antimycotic agent that is in clinical use since the 1970s. It has a broad antimycotic action spectrum, which includes dermatophyte species, yeasts (*Candida* spp., *Malassezia* spp.) and other fungi (Piérard et al. 2012, WellSpring 2020). Miconazole has a dual mechanism of action. Like all azoles, it inhibits lanosterol demethylase, thereby inhibiting ergosterol synthesis. In addition, miconazole increases intracellular reactive oxygen species, at least in part through inhibition of fungal catalase and peroxidase (Musaji 2010). Miconazole is used topically/locally to treat common fungal infections, such as athlete's foot, jock itch, *tinea corporis*, *tinea versicolor*, cutaneous candidiasis, oropharyngeal candidiasis and vaginal yeast infections (Piérard et al. 2012, WellSpring 2020). It is available in different forms, including vaginal suppository, cream, oromucosal gel, mucoadhesive formulations, powder and spray (in a strength of ≤ 2%) (TGA 2014). Miconazole preparations are available over the counter in many countries. A combination consisting of miconazole and hydrocortisone is also available as OTC product for the treatment of certain skin conditions, particularly fungal infections with associated inflammation and itching. The combination of miconazole and hydrocortisone is typically available in the form of creams or ointments for topical application.

Primary and secondary resistance to miconazole

Resistance of miconazole to dermatophytes is rare (Khatri et al. 2017). Moreover, miconazole still shows good activity against most *Candida* species (Miranda-Cadena et al. 2018). The prevalence of miconazole resistance among Candida species can vary between different studies and geographic regions. For example, studies have reported miconazole resistance rates ranging from less than 1% to around 20% (in India) among *Candida* isolates causing vaginal or oral yeast infections (Taghipour et al. 2018, Barot et al. 2019, Kessler et al. 2022, Verma et al. 2021). *Candida krusei* is intrinsically less susceptible to miconazole compared to other *Candida* species. The presence of concomitant systemic comorbidities appears to be an essential factor that should be considered when evaluating resistance to antifungals for oral isolates (Kessler et all 2022).

Resistance has been associated with the overexpression of efflux pump genes, change in the miconazole target, ergosterol biosynthesis pathway alteration, efflux pump overexpression, altered membrane composition, increased drug metabolism and enhanced DNA repair mechanisms (Berkow et al. 2020).

Terbinafine

Terbinafine is an allylamine antimycotic agent that is in clinical use since the 1990s. It used for the treatment of fungal infections of the skin and nails caused by dermatophytes such as *Trichophyton*, *Microsporum canis*, *Epidermophytpon flocossum* and yeasts of the genus *Candida* as well as *Malassezia furfur* (Novartis 2023). Terbinafine is used topically for superficial skin infections such as jock itch (*tinea cruris*), athlete's foot (*tinea pedis*) and other types of ringworm (*tinea corporis*). Tablets are used for the treatment of onychomycosis. Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine inhibits the squalene epoxidase in the fungal cell membrane. Terbinafine is available as oral (tablet) and topical formulations (cream, spray, gel, lotion, lacquer). Topical preparations are available over the counter (in a strength of ≤ 1%).

Primary and secondary resistance to terbinafine

Terbinafine resistance is relatively infrequent. Resistance has been documented in *Trichophyton* isolates particularly in India but also Europe (Khatri et al. 2017, Astvad et al. 2022, Bermudez et al. 2023). The main etiological agents of dermatophytosis of skin and nails in humans are *T. rubrum*, *T. interdigitale* and *T. mentagrophytes* for which the resistance rates to terbinafine are still low (Monod and Méhul 2019, Moreno-Sabater et al. 2022). The emerging dermatophyte *T. indotineae* has become a concern in dermatology; it spread globally from the Indian subcontinent. In a recent French multicenter study, terbinafine resistance frequency was 0.23%, 1.1% and 16.7% for *T. rubrum*, *T. interdigitale* and *T. indotineae* isolates, respectively, with the caveat that the number of *T. indotineae* isolates was low (Moreno-Sabater et al. 2022).

Terbinafine resistance has been predominantly attributed to point mutations in the squalene epoxidase gene whose product is the drug target for terbinafine (Gupta and Venkataraman 2022). Primary resistance to terbinafine is relatively uncommon but has been reported in some studies (Lagowski et al. 2020).

Resistance to terbinafine and other allylamines is very rare and usually correlated with point mutations in the squalene epoxidase gene resulting in single amino acid substitutions in the enzyme, which is crucial in the er-

gosterol synthesis pathway. However, there are also considerations that this development might be due to intrinsic point mutations instead of a drug-exposure-acquired phenomenon. Terbinafine has been reported to be the most effective antifungal agent against Trichophyton spp. isolates worldwide (Ryder et al 1992).

Optimal adherence is very important for therapeutic success in treatment of mycotic infections. The longer the treatment the higher the risk of loss of patient adherence (Łagowski et al 2020).

A change of prescription status would result in delayed treatment onset with the risk of prolonged infection including chronification with all negative consequences for the patient and health economy (Nenof 2022). Additionally, the instructions for use for the patient contain the recommendation to consult a physician or the pharmacist in case of persisting symptoms.

Amorolfine

Amorolfine is a topical morpholine antifungal that is in clinical use since the 1990s. It is commonly available in the form of a nail lacquer, containing up to 5% of amorolfine hydrochloride. It is used to treat onychomycoses caused by dermatophytes, yeast and moulds without matrix involvement (Flagothier et al. 2005, PAR 2011). Amorolfine is applied directly to the affected nails allowing the drug to penetrate and act on the underlying fungal infection. Amorolfine is a broad spectrum antimycotic. Among others, it is highly active against yeasts (*Candida, Cryptococcus, Malassezia*), dermatophytes (*Trichophyton, Microsporum, Epidermophyton*) and moulds (*Scopulariopsis*) (PAR 2011, Jain et al. 2022). Its fungicidal action is based on an alteration of the fungal cell membrane targeted primarily on sterol biosynthesis. The ergosterol content is reduced and at the same time unusual sterically nonplanar sterols accumulate. That means, it has a dual mechanism of action (Chandra et al. 2019, Jain et al. 2022). Topical amorolfine is approved for sale over the counter in various countries.

Primary and secondary resistance to amorolfine

Resistance to amorolfine is rare. It may develop upon long-term and repetitive use, especially when it is not used correctly with prolonged exposure to sub-inhibitory amorolfine concentrations and incomplete eradication of the pathogen (Jiang et al. 2021). Primary resistant variants of sensitive fungal species have rarely been reported (Gupta and Venkataraman 2022). The development of secondary resistance by susceptible fungi has only rarely been reported so far (e.g. for *Trichophyton rubrum*) (Ghelardi et al. 2014, Jiang et al. 2021). Susceptibility testing is usually not recommended (Ghelardi et al. 2014).

It has been suggested that resistance of dermatophytes to amorolfine is due to increased drug efflux by overexpression of ATP-binding cassette transporters (Ghelardi et al. 2014).

Ciclopirox olamine

Ciclopirox olamine (CPO) is a synthetic topical antifungal of the hydroxypyridone family that is in clinical use for over three decades. CPO is a hydroxypyridone derivative that differs in structure and mechanism of action from the other known antifungal agents (Sonthalia et al. 2019). It acts through the chelation of polyvalent metal cations, such as ferric (Fe3+) and aluminum (Al3+), thereby causing inhibition of metal□dependent enzymes leading to disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across the cell membrane. CPO has also been known to alter membrane permeability causing blockage of intracellular transport of precursors (GlaxoSmithKline 2018, Sonthalia et al. 2019). Ciclopirox is the active compound, with no additional antifungal contribution by the olamine salt. CPO expresses a broad spectrum of antimycotic activity and inhibits nearly all clinically relevant dermatophytes, yeasts and moulds, including *Candida glabrata* and *Candida krusei*. CPO can be both fungistatic and fungicidal depending on the concentration and the duration of contact with target organisms (Sonthalia et al. 2019, Falotico and Liner 2022). Important in its efficacy in the treatment of dandruff/seborrheic dermatitis and other mild dermatoses is that CPO is an effective antifungal against *Pityrosporum ovale* and *Pityrosporum orbiculare*. The latter are the yeast forms of *Malassezia furfur*, which have been implicated as the causative organisms in conditions such as dandruff (GlaxoSmithKline 2018). It is available as OTC product in the form of a nail lacquer (for onychomycosis), shampoo (for seborrheic dermatitis) and cream/gel/spray (for dermatophytic and yeast infections of the skin) (Sonthalia et al. 2019).

Primary and secondary resistance to ciclopirox olamine

Despite its frequent use over decades, the resistance situation for CPO is very low. According to Sonthalia et al. (2019), not even a single case of clinical or in vivo resistance has been reported by 2019. The potential of dermatophytes for developing resistance to CPO by biochemical or molecular means is considered extremely low (Sonthalia et al. 2019). Similarly, Gupta and Venkataraman (2022) noted that CPO has not shown any potential resistance development in *T. rubrum* to date. Interestingly, despite multiple exposures of *T. rubrum* to subinhibitory concentrations of CPO, no mutant resistant strains could be isolated (Rosen 2016). The most plausible reasons behind the inability of superficial fungi (both dermatophytes and yeasts) of mounting or evolving mechanisms to resist CPO are its fungicidal mode of action, unique anti-fungal mechanism of action and a steep dose-response curve (Gupta and Plott 2004, GlaxoSmithKline 2018, Sonthalia et al. 2019).

Econazole

Econazole is a broad spectrum imidazole antimycotic agent that is in clinical use since the 1970s. It has a wide antimycotic action spectrum, which includes dermatophyte species, yeasts and moulds. Econazole (in its nitrate form) is used for topical application in the treatment of *tinea pedis*, *tinea cruris* and *tinea corporis* caused by certain dermatophytes, in the treatment of cutaneous candidiasis and in the treatment of *tinea versicolor* (SmPC 2017). In some countries, econazole is also sold as vaginal ovule to treat vaginal thrush (SmPC 2021). The compound acts by damaging the membranes of bacterial and fungal cells. Both the cellular and subcellular membranes are affected. Econazole apparently disturbs the permeability characteristics of the membrane which allow leakage of potassium and sodium ions and other intracellular components. Macromolecular synthesis may also be inhibited (SmPC 2021). It is available as different topical/local formulations, including cream, lotion, powder and vaginal ovule. Econazole preparations are available over the counter in many countries.

Primary and secondary resistance to econazole

Primary resistance to econazole is uncommon. The development of secondary resistance by susceptible fungi has only rarely been documented so far. The prevalence of econazole resistance among *Candida* species can vary between different studies and geographic regions. For example, studies have reported econazole resistance rates ranging from less than 1% among *Candida* strains isolated from superficial infections (Abastabar et al. 2015) to around 25% among *Candida* isolates isolated from human oral cavities (Kessler et al. 2022). In a recent Mexican study, Lomeli-Martinez et al. (2022) determined the *in vitro* azole antifungals susceptibility of *Candida* spp. strains isolated from HIV-positive patients with periodontitis. In these HIV-positive patients, econazole and miconazole presented the highest susceptibility rates with 63.2% and 63.7% isolations, respectively. This is noteworthy because the *Candida* spp. involved in periodontitis of HIV-positive patients have a multi-resistant feature. Econazole also showed a favourable susceptibility pattern activity against non□dermatophyte (saprophytic) molds causing onychomycosis in a recent evaluation of antifungal activities (96% of the samples were sensitive) (Pakshir et al. 2021).

Resistance has been associated with the overexpression of efflux pump genes, change in the econazole target, efflux pump overexpression, altered membrane composition, increased drug metabolism and enhanced DNA repair mechanisms (Berkow et al. 2020).

Ketoconazole

Ketoconazole is an imidazole antimycotic agent that is in clinical use since the early 1980s. Topical formulations (e.g. shampoo, cream, ointment) are available as OTC products to treat fungal skin infections (e.g. *tinea*, scalp dandruff, seborrheic dermatitis). In some countries, only the shampoo is available over the counter. Ketoconazole has a wide antimycotic action spectrum; it inhibits the growth of common dermatophytes, yeasts and other fungi by interacting with ergosterol synthesis that results in alteration of the permeability of the cell membrane (Teva 2014, Dall'Oglio et al. 2022, Carmo et al. 2023). In 2013, the review of available data on the efficacy and safety of ketoconazole-containing medicines for oral use by the European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) recommended the suspension of the marketing authorizations of oral ketoconazole-containing medicines throughout the EU. The CHMP concluded that the

risk of liver injury upon oral use is greater than the benefits of treating fungal infections, but the topical use of ketoconazole remains favourable as the amount of ketoconazole absorbed is very low with these formulations (Carmo et al. 2023).

Primary and secondary resistance to ketoconazole

Primary resistance to ketoconazole is uncommon. The development of secondary resistance by susceptible fungi has been primarily reported for some *Candida* species following prolonged treatment (Teva 2014). The prevalence of ketoconazole resistance among *Candida* species can vary between different studies and geographic regions. For example, studies have reported ketoconazole resistance rates ranging from less than 1% to ≥20% (in India or Africa) among *Candida* isolates (Tsega and Mekonnen 2019, de Oliveira and Schmidt 2021, Zarrinfar et al. 2021, Verma et al. 2021, Wu et al. 2021). Resistance has been associated with multiple factors including efflux pump overexpression and genetic mechanisms (Xu et al. 2021).

Resistance of ketoconazole to dermatophytes and fungi associated with scalp dandruff and seborrheic dermatitis is rare (Mahajan et al. 2017, Park et al. 2020). Ketoconazole is still used as reference drug in the evaluation of new antifungal OTC preparations (Pona et al. 2020).

Clinical consequences

Cases of invasive fungal disease are rising. This rise is directly linked to the rise in the number of immunocompromised people as a result of changes in medical practice, such as the use of powerful immunosuppressive medications and intense chemotherapy (WHO 2022, Hossain et al. 2022, Mc Dermott 2022). Currently, four classes of systemic antifungal medicines (azoles, echinocandins, pyrimidines and polyenes) are used in clinical practice, with the observation that pathogenic fungi are evolving resistance to all licensed systemic antifungal drugs (Fisher et al. 2022). WHO performed a prioritization process on fungal pathogens that can cause invasive acute and subacute systemic fungal infections for which drug resistance or other treatment and management challenges exist. The critical group included *Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus* and *Candida albicans* (WHO 2022).

Already in 2000, Cross et al. (2000) raised the concern that the frequent use of OTC azole antifungals for local *Candida* infections may promote the development of azole resistance by contributing to the selection of resistant strains of *Candia* in otherwise healthy subjects, and that this may also be true for systemically applied azoles (e.g. fluconazole, itraconazole, voriconazole, posaconazole) due to cross-resistance mechanisms.

More than 20 years later, it can be claimed that upon use of antifungals in the approved indications and according to the product information, the prescription-free use can be considered safe for humans, as exemplified by clotrimazole or bifonazole. Despite its use over many years, clotrimazole resistance is rare in the general population. In fact, one of the best methods to avoid acquiring resistance is to take antifungal medication as directed (Hossain et al. 2022).

The risk of resistance development to antifungals exists if the antifungals are used inappropriately, especially during long courses of systemic treatment with persistently low drug concentrations in the systemic circulation and tissues (Perlin et al. 2017, Fisher et al. 2022, Carmo et al. 2023). In addition, the widespread prophylactic and empiric prescribing of antifungals to treat suspected invasive fungal diseases in individuals who are chronically at risk, those who are critically ill and in patients with haemato-oncologic diseases remains a concern (Fisher et al. 2022). Antifungal resistance can also be acquired by other factors (e.g. poor patient compliance, when doses are skipped, therapy is stopped too soon, or the dose is too low) (Pai et al. 2018, Hossain et al. 2022, Gupta and Venkataraman 2022, Baid 2022). The American Society for Microbiology and others consider overuse of fungicides in agriculture and improper disposal of antifungal drugs also as drivers of resistance (Perlin et al. 2017, Baid 2022, Carmo et al. 2023).

Is the proposed risk minimization measure (i.e. prescription) the most effective mechanism?

Switching OTC antifungal drugs back to prescription drugs would not only burden the health care system to an unpredictable extent, it would also prevent patients from having full and reliable access to health care resources in the presence of minor conditions they can take care of themselves. Nowadays, the importance of self-care/"health care in your own hands", health literacy, knowledgeable patient/consumer, lifting burden on healthcare systems, etc. is emphasized by various parties and institutions. Switching back to compulsory prescription would achieve exactly the opposite with feeling patients to have been disempowered to take care of themselves - superfluously, since the risk of resistance development is evidently low for OTC antifungals.

One of the foreseen consequences when switching back to RX, would be going back to the days of relying on ineffective home remedies. The result would be an unnecessary protraction of the disease, increased suffering (or even worsening) for the patient and extra work for the doctor with an increased burden on the health care system. Potentially needing to get systemic products while an effective and localized solution would already be available in the market. Quick treatment is mandatory for minor conditions (e.g. *tinea inguinalis*) before it spreads (e.g. to the genital area).

In fact, upon correct use of antifungals, the prescription-free use is safe for humans. Despite its use over many years, resistance rates for OTC antifungals are generally low. One of the best methods to avoid acquiring resistance is to take antifungal medication as directed (Hossain et al. 2022). Hence, appropriate education programmes for HCPs/patients have to be set up to achieve the latter.

Risk reduction strategies aimed at minimizing the emergence of resistance to OTC antifungals may include the following approaches.
For Portugal, the second biggest consumer of OTC antifungals in Europe, a research group from Porto recommended to engage physicians and pharmacists to provide educational information to the general public about antifungal drugs consumption. Pharmacists and other pharmacy staff should receive continuing education about how to control the spread of infections and antimicrobial resistance. This would improve their counselling of patients exhibiting characteristic signs and symptoms of fungal infections. With regard to general stores and supermarkets, it was proposed to implement measures to improve staff knowledge (e.g. interactive educational workshops for the workers involved) (Manuel da S Azevedo et al. 2016).

Educational programs could limit antifungal medication misuse and improve patient compliance. Specifically, consumers must be careful about how they dispose of drugs and have to follow correct dosing regimens. Most importantly, they should ensure to take the entire regimen of antifungals to ensure complete killing of the pathogen and prevent the rise of resistance (Perlin et al. 2017, Baid 2022).

Having seen that one of the potential reasons for antifungal resistance is treatment adherence, prescription status would not change this in a positive way.

Generally, because invasive fungal diseases are most common in immunocompromised hosts, host-directed approaches are needed to lessen the pressure on antifungal drugs (Fisher et al. 2022, Rabaan et al. 2023). Immunocompromised patient are monitored by their physicians and therefore there is clearly a role for doctors towards education and reminding of importance of compliance.

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About

The Association of the European Self-Care Industry (AESGP) is a non-profit organisation which represents the manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe, an area also referred to as consumer healthcare products.

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