95/95 BY 2025

ENSURE THAT BY 2025 95% OF PEOPLE WITH SERIOUS FUNGAL DISEASE ARE DIAGNOSED AND 95% TREATED = 95-95

Appendix 5

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

The first active antifungal agents were developed in the 1950's (amphotericin B, nystatin, griseofulvin and flucytosine), with key additions in the 1980's and 90's (ketoconazole, fluconazole, itraconazole and lipid amphotericin B formulations). Since the millennium, improved azoles (voriconazole and posaconazole) and the echinocandins (caspofungin, micafungin, and anidulafungin) have appeared, as well as many other topical agents.

A summary of antifungal therapy, and detailed information on each available agent is available here:

www.life-worldwide.org/fungal-diseases/antifungal-agents

Other aspects of therapy including the use of corticosteroids, surgery, immunotherapy and bronchial artery embolisation are provided here:

www.life-worldwide.org/fungal-diseases/treatment

Antifungal resistance

Antifungal resistance is a more substantial problem than it used to be. Some fungi are intrinsically resistant to certain antifungals; notably *Candida krusei* to fluconazole, *Aspergillus terreus* to amphotericin B, *Cryptococcus* spp. to the echinocandins and *Scedosporium* spp. to all current antifungals. Most *Candida* isolates are fluconazole susceptible, but a recent large study from India, as an example, showed 12% to be fluconazole resistant and a similar picture is emerging in China. *Candida glabrata* is especiallyy problematic being the second most commonly isolated Candida species in the EU (>10%) and USA (>20%) with high rates of resistance to fluconazole and voriconazole and recent emergence of echinocandin resistance.

Both azole and echinocandin resistance are increasingly troublesome and rapid development of antifungal resistance with 5FC is problematic with cryptococcal meningitis.

Azole resistance in *Aspergillus* is a significant and growing problem particularly in the Netherlands where azole resistant A. fumigatus is now commonplace (7% of all clinical isolates) (30). Multi-azole resistance in *Aspergillus* has been detected in clinical or environmental samples in Belgium, Denmark, Sweden, Germany, Spain, France, UK, USA, Canada and also in China, India, Tanzania, Kuwait and Iran. Outcomes from invasive aspergillosis with a resistant strain are poor – nearly a 90% mortality against an expected mortality in invasive aspergillosis of ~50%. In the future direct molecular detection of resistance markers will become clinical reality as many fungi do not grow in culture.

Deficiencies in available therapy

Other key deficiencies include a lack of oral preparations of echinocandins, the drug of choice for many *Candida* infections, unnecessarily prolonging hospitalization and intravenous therapy.

Drug interactions are a major problem for the azoles, especially voriconazole and itraconazole. Certain drug toxicities are treatment limiting or dangerous, notably renal dysfunction on amphotericin B treatment, and liver function abnormalities with the azoles.

The relative bioavailability of different generic formulations of itraconazole is not well documented, partly because the primary focus is on manufacturing standards and data from patients is not required by any regulator.

Above. Pharmacy in Central Beijing,China

Appendix 5/2

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

Table 5.1 SWOT analysis of current antifungal agents for all forms of aspergillosis

Strengths

- IV and oral formulations
- All species susceptible to latest generation triazoles (voriconazole, posaconazole and isavuconazole)
- Improved survival of voriconazole and isavuconazole compared with all other antifungal agents
- Low adverse event profile for echinocandins and posaconazole and isavuconazole

Weaknesses

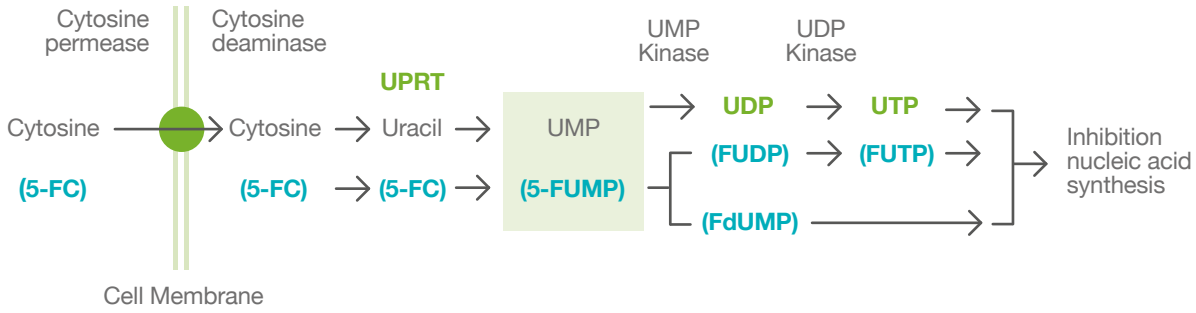
- Oral formulations only triazoles
- *A. terreus* and *A. nidulans* resistant to amphotericin B
- *A. niger* resistant to itraconazole
- Emerging triazole resistance in *A. fumigatus*
- Adverse events with itraconazole, voriconazole and amphotericin B problematic
- Multiple drug interactions for triazoles, notably itraconazole and voriconazole
- Marked interpatient variability with triazoles, justifying therapeutic monitoring of blood concentrations
- Cost excessive for long term usage
- Usage and monitoring difficult in those with liver dysfunction

Opportunities

- Licensing for additional long term indications, such as chronic and allergic aspergillosis
- Inhaled antifungal agents for allergic aspergillosis, *Aspergillus* bronchitis and prophylaxis
- Development of agents with different price points for long term usage
- Agents with improved survival advantage and reduced toxicity
- Combination treatment for initial therapy and long term treatment to prevent triazole resistance
- Reduced drug interactions

Threats

- Increasing airborne spread of triazole resistance in *A. fumigatus* across the world
- Triazole resistance emerges in other species
- Poor quality generic products, with limited bioavailability
- Rapid resistance emergence for new compounds, especially if same chemistry used as an agricultural fungicide
- Complexity and length of clinical trial program for invasive aspergillosis (and many other fungal infections) with current agents being freely used. This is a problem for many fungal infections not only aspergillosis.



Above. Flucytosine (5-FC) is a subversive substrate within the pyrimidine salvage pathway. The normal pathway and the toxic fluorinated metabolites are shown. Fluorinated nucleotides lead to disruption of nucleic acid synthesis (99)

Appendix 5/3

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

New antifungal pipeline

The pipeline for new antifungal drugs is sparse, at best. Currently, there are only 6 compounds in active clinical development for the treatment of systemic fungal disease (Table 5.2). Two other agents expected to enter clinical development in 2015. A few other compounds are in pre-clinical development. Of note, few compounds are novel chemistries with different modes of action from the current marketed agents. Not all will progress to clinical studies.

Table 5.2 Antifungals in late preclinical, phase 1, phase 2 or phase 3 development.

Name	Company	Spectrum	Route	Mode of Action	Stage	Comments
Isavuconazole	Basilea	Broad spectrum	IV/Oral	14 alpha demethylase inhibition	FDA approved, not launched	Invasive aspergillosis and candidiasis, mucormycosis
Albaconazole	Actavis	Broad spectrum	IV/oral	14 alpha demethylase inhibition	II	Vulvovagingal candidiasis and onychomycosis
Scy078 (MK-3118)	Scynexis	Broad spectrum	IV/oral	Glucan synthase inhibitor	IIa	Phase II development on candidiasis
VT1161	Viamet	*Candida* spp/ dermatophytes/	Oral/ topical	14 alpha demethylase inhibition	II	Phase II trials ongoing for VVC and tinea pedis
VT1129	Viamet	*Cryptococcus*	Oral/IV	14 alpha demethylase inhibition	Pre-I	Preclinical, pending funding
Nikkomycin Z	Valley Fever Solutions	*Coccidioides*	Oral	Chitin synthesis inhibitor	II	Phase II pending
F901318	F2G	Moulds	Oral/IV	Novel, not disclosed	I	Aspergillosis, other mould infections

Discovery and development impediments

The intrinsic challenge of identifying new active compounds and a chronic lack of investment in novel antifungal agents are both responsible for a sparse pipeline. Few major pharmaceutical companies are investing in the development of new agents, preferring to acquire new compounds from biotech, or invest in other areas. This had led many commentators to state that the current model for R&D investment in this area is broken due to a lack of adequate market incentives. Significant effort has been made to identify potential solutions to this problem including reducing or offsetting R&D costs by pump priming public-private partnerships through research grants (e.g. the Innovative Medicines Initiative IMI), reducing clinical trial complexity, extending market exclusivity (e.g. the GAIN act in which *Aspergillus, Candida* and *Cryptococcus* spp. are named specifically) and decoupling revenues from unit sales (to increase overall revenues). Although some of these ideas have yet to be rationalized, those that have been implemented have failed to filter into antifungal R&D. For example of the 2 billion euro IMI (EU) budget and the R&D funded by the BARDA Broad Spectrum Antimicrobials program, not a single project has been funded to support the development of novel antifungals.

Above. Some examples of the 3 oral antifungal agents useful in the treatment of aspergillosis – itraconazole, voriconazole and posaconazole.

Appendix 5/4

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

Key generic antifungal drug availability and registration by country

GAFFI has collected data on registration and availability of the older generic antifungals from multiple sources including the WHO, MSH and primarily from individuals in each country who established which preparations of which antifungal was or was not available locally. The data and information about the number of generics available, and local price are shown graphically below in Table 5.3. and here: www.gaffi.org/why/burden-of-disease-maps

Table 5.3 Registration and availability of fluconazole (outside the Pfizer donation program), itraconazole, amphotericin B and flucytosine in each country with a population > 1 million.

Country	Key generic antifungal drug drug availability by country							
	Fluconazole		Itraconazole		Amphotericin B		Flucytosine	
	Registered	Available	Registered	Available	Registered	Available	Registered	Available
Afghanistan	Y	N	N	N	Y	N	N	N
Albania	Y	Y	Y	Y	N	N	N	N
Algeria	N	N	N	N	Y	Y	N	N
Angola	ND	ND	ND	ND	N	N	N	N
Argentina	Y	Y	Y	Y	Y	Y	Y	N
Armenia	Y	ND	ND	ND	Y	ND	Y	ND
Australia	Y	Y	Y	Y	Y	Y	Y	Y
Austria	Y	Y	Y	Y	Y	Y	Y	Y
Azerbaijan	ND	ND	ND	ND	N	N	ND	ND
Bahrain	Y	ND	ND	ND	N	N	ND	ND
Bangladesh	Y	Y	Y	Y	N	N	N	N
Belarus	Y	Y	Y	Y	Y	Y	N	N
Belgium	Y	Y	Y	Y	Y	Y	N	N
Benin	ND	ND	ND	ND	Y	Y	N	N
Bolivia	Y	Y	ND	ND	N	N	ND	ND
Bosnia & Herzegovina	Y	Y	Y	Y	N	N	N	N
Botswana	Y	Y	Y	Y	Y	Y	N	N
Brazil	Y	Y	Y	Y	Y	Y	Y	N
Bulgaria	Y	Y	Y	Y	Y	Y	N	N
Burkina Faso	ND	ND	ND	ND	Y	N	N	N
Burundi	ND	ND	ND	N	Y	N	N	N
Cambodia	ND	ND	ND	ND	N	N	ND	ND
Cameroon	Y	Y	ND	ND	N	N	N	N
Canada	Y	Y	Y	Y	Y	Y	N	N
Central African Republic	ND	ND	ND	ND	Y	N	N	N
Chad	ND	ND	ND	ND	Y	N	N	N
Chile	Y	Y	Y	Y	Y	Y	N	N
China	Y	Y	Y	Y	Y	Y	Y	Y
Hong Kong	Y	Y	Y	Y	Y	Y	Y	Y
Colombia	Y	Y	Y	Y	Y	Y	Y	Y

KEY. **Y**= Yes **N** = NO **ND** = No Data

Appendix 5/5

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

Country	Key generic antifungal drug drug availability by country							
	Fluconazole		Itraconazole		Amphotericin B		Flucytosine	
	Registered	Available	Registered	Available	Registered	Available	Registered	Available
Congo	ND	ND	ND	ND	Y	N	N	N
Costa Rica	Y	Y	ND	ND	Y	Y	ND	ND
Côte d'Ivoire	ND	ND	ND	ND	Y	N	N	N
Croatia	Y	Y	Y	Y	Y	Y	Y	ND
Cuba	Y	Y	Y	Y	Y	Y	Y	Y
Czech Republic	Y	Y	Y	Y	Y	Y	N	N
North Korea	ND	ND	ND	ND	N	N	ND	ND
Dem. Rep. Congo	Y	Y	Y	Y	Y	Y	N	N
Denmark	Y	Y	Y	Y	Y	Y	Y	Y
Dominican Republic	Y	Y	Y	Y	Y	N	N	N
Ecuador	Y	Y	Y	Y	Y	ND	N	N
Egypt	Y	Y	Y	Y	Y	Y	N	N
El Salvador	Y	Y	Y	Y	Y	N	ND	ND
Equatorial Guinea	ND	ND	ND	ND	N	N	N	N
Eritrea	ND	ND	N	N	Y	N	N	N
Estonia	Y	Y	Y	Y	N	N	ND	ND
Ethiopia	Y	Y	Y	Y	Y	Y	N	N
Finland	Y	Y	Y	Y	Y	Y	N	N
France	Y	Y	Y	Y	Y	Y	Y	Y
Gabon	ND	ND	ND	ND	N	N	N	N
Gambia	Y	Y	N	N	N	N	N	N
Georgia	Y	Y	Y	Y	Y	Y	ND	ND
Germany	Y	Y	Y	Y	Y	Y	Y	Y
Ghana	Y	ND	ND	ND	N	N	N	N
Greece	Y	Y	Y	Y	Y	Y	Y	Y
Guatemala	Y	Y	Y	Y	Y	Y	N	N
Guinea	ND	ND	ND	ND	N	N	N	N
Guinea-Bissau	ND	ND	ND	ND	N	N	N	N
Haiti	Y	ND	ND	ND	N	N	ND	ND
Honduras	Y	Y	Y	Y	N	N	ND	ND
Hungary	Y	Y	Y	Y	Y	Y	ND	ND
India	Y	Y	Y	Y	Y	Y	Y	Y
Indonesia	Y	Y	Y	Y	Y	N	N	N
Iran	Y	Y	Y	Y	Y	Y	Y	Y
Iraq	Y	Y	Y	Y	Y	Y	Y	Y
Ireland	Y	Y	Y	Y	Y	Y	Y	Y
Israel	Y	Y	Y	Y	Y	Y	N	Y (limited)
Italy	Y	Y	Y	Y	Y	Y	N	N

KEY. **Y**= Yes **N** = NO **ND** = No Data

Appendix 5/6

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

Country	Key generic antifungal drug drug availability by country							
	Fluconazole		Itraconazole		Amphotericin B		Flucytosine	
	Registered	Available	Registered	Available	Registered	Available	Registered	Available
Jamaica	ND	ND	Y	Y	N	N	ND	ND
Japan	Y	Y	Y	Y	Y	Y	Y	Y
Jordan	Y	Y	Y	Y	Y	Y	N	N
Kazakhstan	Y	Y	Y	Y	N	N	ND	ND
Kenya	Y	Y	Y	Y	Y	Y	N	N
Republic of Korea	Y	Y	Y	Y	Y	Y	Y	Y
Kuwait	ND	ND	ND	ND	N	N	ND	ND
Kyrgyzstan	Y	ND	ND	ND	Y	N	ND	ND
Laos	Y	Y	Y	Y	Y	Y	ND	ND
Latvia	Y	Y	Y	Y	Y	Y	ND	ND
Lebanon	Y	Y	Y	Y	Y	Y	N	N
Lesotho	Y	ND	ND	ND	Y	N	N	N
Liberia	ND	ND	ND	ND	N	N	N	N
Libya	Y	Y	Y	Y	Y	Y	N	N
Lithuania	Y	Y	Y	Y	Y	N	ND	ND
Macedonia	ND	ND	ND	ND	N	N	ND	ND
Madagascar	Y	N	Y	N	Y	N	N	N
Malawi	Y	Y	Y	Y	Y	Y	N	N
Malaysia	Y	Y	Y	Y	Y	Y	N	N
Mali	Y	ND	ND	ND	Y	N	N	N
Mexico	Y	Y	Y	Y	Y	Y	N	N
Republic of Moldova	Y	ND	ND	ND	N	N	ND	ND
Mongolia	Y	Y	N	N	N	N	N	N
Morocco	Y	ND	ND	ND	Y	N	ND	ND
Mozambique	Y	Y	Y	Y	N	N	N	N
Myanmar	Y	ND	Y	Y	ND	ND	ND	ND
Namibia	Y	Y	Y	Y	Y	N	N	N
Nepal	Y	Y	Y	Y	Y	Y	N	N
Netherlands	Y	Y	Y	Y	Y	Y	Y	Y
New Zealand	Y	Y	Y	Y	Y	Y	N	N
Nicaragua	Y	Y	Y	Y	N	N	ND	ND
Niger	ND	ND	ND	ND	N	N	N	N
Nigeria	Y	Y	Y	Y	Y	N	N	N
Norway	Y	Y	Y	Y	Y	Y	ND	ND
Oman	Y	Y	Y	Y	N	N	N	N
Pakistan	Y	Y	N	Y	Y	N	N	N
Palestine	ND	ND	ND	ND	ND	ND	ND	ND
Panama	Y	Y	Y	Y	N	N	ND	ND

KEY. **Y**= Yes **N** = NO **ND** = No Data

Appendix 5/7

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

Country	Key generic antifungal drug drug availability by country							
	Fluconazole		Itraconazole		Amphotericin B		Flucytosine	
	Registered	Available	Registered	Available	Registered	Available	Registered	Available
Papua New Guinea	ND	ND	ND	ND	Y	N	ND	ND
Paraguay	Y	Y	ND	ND	Y	N	ND	ND
Peru	Y	Y	Y	Y	Y	Y	ND	ND
Philippines	Y	Y	Y	Y	Y	Y	N	N
Poland	Y	Y	Y	Y	Y	Y	Y	Y
Portugal	Y	Y	Y	Y	Y	Y	ND	ND
Puerto Rico	ND	ND	ND	ND	N	N	ND	ND
Qatar	Y	Y	Y	Y	Y	Y	Y	Y
Romania	Y	Y	Y	Y	Y	Y	N	N
Russia	Y	Y	Y	Y	Y	Y	Y	Y
Rwanda	Y	Y	Y	Y	Y	Y	N	N
Saudi Arabia	Y	Y	Y	Y	Y	Y	N	N
Senegal	Y	Y	N	N	Y	N	N	N
Serbia	Y	Y	Y	Y	N	N	N	N
Sierra Leone	Y	ND	ND	ND	Y	N	N	N
Singapore	Y	Y	Y	Y	Y	Y	Y	N
Slovakia	Y	Y	Y	Y	Y	N	Y	Y
Slovenia	Y	Y	Y	Y	N	N	ND	ND
Somalia	Y	ND	ND	ND	Y	N	N	N
South Africa	Y	Y	Y	Y	Y	Y	N	N
South Sudan	Y	Y	Y	Y	N	N	N	N
Spain	Y	Y	Y	Y	Y	Y	N	N
Sri Lanka	Y	Y	Y	Y	Y	Y	N	N
Sudan	ND	ND	ND	ND	Y	Y	Y	ND
Swaziland	ND	ND	ND	ND	Y	Y	N	N
Sweden	Y	Y	Y	Y	Y	Y	Y	Y
Switzerland	Y	Y	Y	Y	Y	Y	Y	Y
Syria	Y	ND	ND	ND	Y	N	ND	ND
Taiwan	Y	Y	Y	Y	Y	Y	Y	Y
Tajikistan	ND	ND	ND	ND	Y	N	ND	ND
Tanzania	Y	Y	Y	Y	Y	N	N	N
Thailand	Y	Y	Y	Y	Y	Y	N	N
Timor-Leste	Y	ND	ND	ND	Y	N	ND	ND
Tunisia	Y	Y	Y	Y	Y	Y	ND	ND
Turkey	Y	Y	Y	Y	Y	Y	ND	ND
Turkmenistan	ND	ND	ND	ND	N	N	ND	ND
Uganda	Y	Y	Y	Y	Y	Y	N	N
Ukraine	Y	Y	Y	N	N	N	Y	N

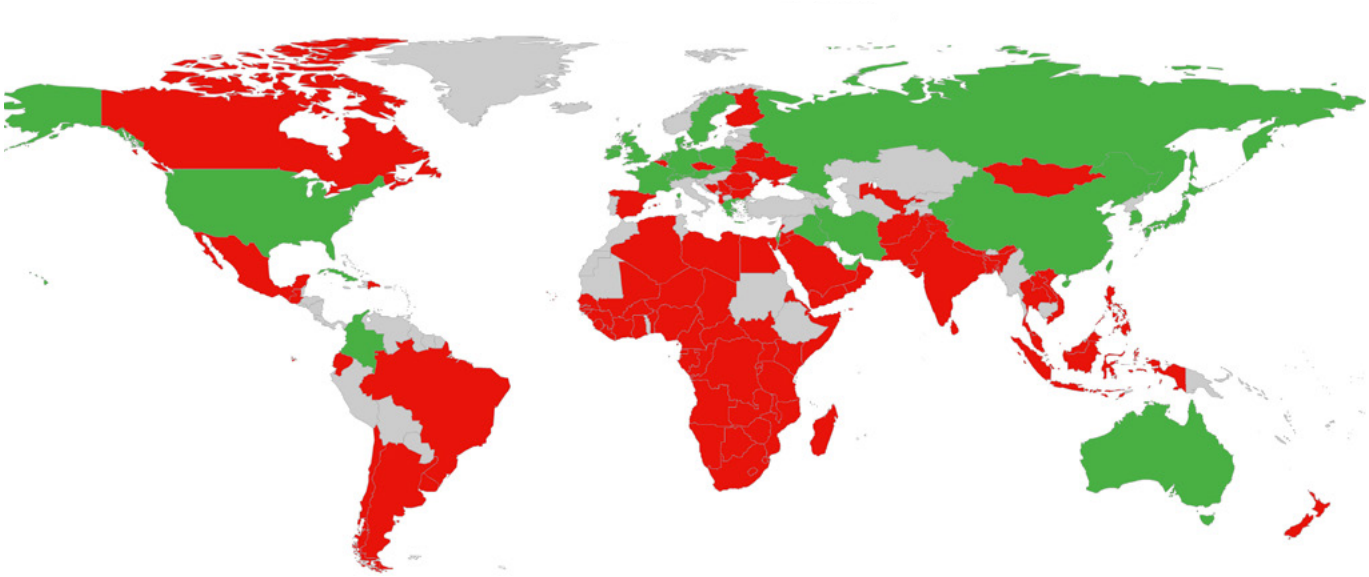
KEY. **Y**= Yes **N** = NO **ND** = No Data

Appendix 5/8

Treatment of Fungal Diseases including development of new antifungal agents, antifungal resistance summary and availability of generic systemic antifungals in each country

Country	Key generic antifungal drug drug availability by country							
	Fluconazole		Itraconazole		Amphotericin B		Flucytosine	
	Registered	Available	Registered	Available	Registered	Available	Registered	Available
UAE	Y	Y	Y	Y	Y	Y	Y	Y
United Kingdom	Y	Y	Y	Y	Y	Y	Y	Y
USA	Y	Y	Y	Y	Y	Y	Y	Y
Uruguay	Y	Y	Y	Y	Y	Y	N	N
Uzbekistan	Y	Y	Y	Y	N	N	N	N
Venezuela	Y	Y	Y	Y	Y	Y	ND	ND
Viet Nam	Y	Y	Y	Y	Y	Y	N	N
Yemen	Y	Y	Y	Y	N	N	N	N
Zambia	Y	Y	Y	Y	Y	Y	N	N
Zimbabwe	Y	Y	Y	Y	Y	N	N	N

KEY. **Y**= Yes **N** = NO **ND** = No Data



Flucytosine (5FC) availability

Flucytosine is available in 28 countries, unavailable in 82 and unclear in 45. It significantly improves the survival in cryptococcal meningitis, when combined with amphotericin B or high dose fluconazole.

Key

Available

Not available

No data