APPLICATION TO ADD NATAMYCIN TO THE ESSENTIAL LIST OF MEDICINES FOR TREATMENT OF FUNGAL KERATITIS

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2. Summary statement of the proposal for inclusion, change or deletion

2.1. Summary of findings

Currently, there are no topical antifungal ophthalmic preparations on the WHO List of essential medicines (WHO EML) for the treatment of fungal corneal infections (keratitis). Infections with filamentous fungi, such as *Fusarium spp.* and *Aspergillus spp.,* are relatively common clinical problems, particularly in tropical regions. They are challenging to treat and outcomes are frequently poor, partly as a result of limited availability of effective medication. In the absence of effective and timely treatment fungal keratitis frequently causes such extensive damage so that the eye is rendered irreversibly blind or has to be removed altogether.

Natamycin 5% topical ophthalmic solution has been widely used for more than forty years in the treatment of fungal keratitis caused by filamentous organisms (1). Recent trials indicate it to be superior to alternative treatment. This application recommends the inclusion of natamycin 5% ophthalmic solution onto the EML for adults and the EML for children.

2.1.1. Clinical studies with Natamycin

We identified seven clinical trials in which patients with fungal keratitis were randomly allocated to receive natamycin ophthalmic solution as one of the treatment arms. There were three trials which compared natamycin 5% to voriconazole 1% (2-4). Overall, these indicate that natamycin is more effective than voriconazole. Natamycin treatment was associated with better visual acuity outcomes, fewer corneal perforations and corneal transplants, more rapid clearing of infection and smaller corneal scars on resolution.

A trial comparing natamycin and econazole found no significant difference, although this was probably underpowered for this comparison (5). Two trials compared natamycin to chlorhexidine. These suggested a possible trend towards more favourable responses with chlorhexidine. However, these studies used several different concentrations of both drugs (including half the standard strength of natamycin) and were relatively small in size (6, 7). Therefore, the relative effectiveness of these two treatments remains uncertain.

3. Name of the WHO technical department and focal point supporting the application

(where relevant)

- Not applicable

4. Name of the organization(s) consulted and/or supporting the application

- Global Action Fund for Fungal Infection, Rue de l'Ancien-Port 14 1211 Geneva 1, Switzerland, in association with the International Centre for Eye Health, Faculty of Infectious & Tropical Diseases, London School of Hygiene and Tropical Medicine, and The Manchester University
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5. International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

- Natamycin- ATC Code: S01AA10

6. Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate)

- Ophthalmic Suspension, 5%

7. Whether listing is requested as an individual medicine or as a representative of a pharmacological class

- Individual medicines under EML section **21.1** (ophthalmological preparations – anti-infective agents)

8. Treatment details (requirements for diagnosis, treatment and monitoring)

8.1. Diagnosis

8.1.1. Clinical Diagnosis

Fungal keratitis should be considered in the differential diagnosis of causes of all cases of microbial keratitis, particularly in tropical regions. Individuals with fungal keratitis typically present with a sub-acute course, with symptoms building up gradually over several days and may only present after a week or more (in contrast to the more acute course of bacterial keratitis). A fungal infection should be particularly suspected if the patient reports having experienced trauma to the eye (even minor) with vegetable matter, reports agriculture as their main occupation or reports having used traditional eye medicine.

The symptoms that patients present with are also common in other forms of keratitis: ocular pain, ocular discharge, reduced vision, redness of the eye, swelling of the eye lids. A careful clinical examination of the eyes needs to performed, ideally with a slit lamp biomicroscope. Clinical signs found on examination may overlap with other causes of microbial keratitis (bacteria, *Acanthamoeba* spp, virus). However the following features should particularly alert the clinician to the possibility of fungal keratitis: (i) “feathery” or serrated edges of the corneal stromal infiltrate; (ii) a raised profile with plaque or slough on the surface of the cornea; (iii) satellite lesions; (iv) endothelial inflammatory plaque (on the inner surface of the cornea); (v) hypopyon with an irregular, non-level surface profile; (vi) dark pigmentation in the corneal infiltrate or plaque (8-10).

8.1.2. Microbiological diagnosis

Microbiological diagnosis of fungal keratitis is slow and complicated. Confirmation of the diagnosis is made from corneal scrapings or biopsy, by microscopy and culture (11). Material is then collected aseptically from the base and margin of the ulcer under direct vision through the magnification of a slit-lamp. Usually sterile needles or a Kimura spatula is used for sampling. The material is then transferred to a clean glass microscope slide, flooded with potassium hydroxide and examined for fungal elements by light microscopy. This method is 60-90% sensitive for hyphae depending on the adequacy of the sample and the interpretive skill of the microscopist. Gram staining is less sensitive, except for identification of *Candida* spp. Other staining methods include Giemsa, lactophenol cotton blue, methanamine silver and calcofluor white; all have strengths and weaknesses (11). Biopsy samples may have a slightly higher diagnostic yield. Samples should be cultured on bacterial and fungal media. Fungal growth is typically slow, taking 48 hours to 10 days to become visible. Due to the diversity of fungi cultured from cases of fungal keratitis, examination of cultures by a specialist mycologist is typically necessary to identify the organism (11). *Fusarium* species are the most common, followed by *Aspergillus* spp. and *Candida* spp. Together with *Penicillium* spp., *Alternaria* spp., *Paecilomyces* spp., *Curvularia* spp. and *Bipolaris* spp., these three pathogenic species account for about 90% of cases, with rare fungi (sometimes unidentified) comprising the remainder. Many cultures are negative for bacteria and fungi, sometimes because of prior antimicrobial therapy.

8.1.3. Other diagnostic modalities

PCR is being used in some settings for the detection of fungal infections, however, there is currently no agreed stand protocol for this and many different assays have been reported. Point of care testing for this infection may improve patient outcomes with a more timely diagnosis and initiation of treatment. *In vivo* confocal microscopy allows for the examination of the cornea to the cellular level. It provides an immediate result in the clinic. It has been successfully used to detect filamentous organisms. However, the equipment is expensive and the operator needs to be skilled in performing the scans and experienced in the interpretation of the results (12).

8.2. Indications

- Fungal keratitis, particularly those caused by filamentous organisms.

9. Information supporting the public health relevance

9.1. Epidemiological information on disease burden

Keratitis refers to inflammation (usually an infection) of the normally transparent cornea of the eye, which causes ulceration and gradual opacification of the cornea, initially due to an influx of inflammatory cells and later, due to fibrosis. Microbial keratitis may be caused by bacteria, fungi, viruses or protozoa (inflammation without infection may be due to chemical injury or autoimmune inflammatory pathology) and is the leading cause of unilateral corneal scarring (8, 13).

Over 100 different fungi have been described as causes of fungal keratitis and new pathogens are regularly described (11). However, the common causative agents are *Fusarium* spp., *Aspergillus flavus*, *A. fumigatus* and *Candida albicans* (less common in tropical climates) (11, 14). In warm, humid climates (15), approximately 50% of cases of microbial keratitis are caused by fungi, but in dry, cool climates, 95% of cases are caused by bacteria. The proportion of microbial keratitis cases attributable to fungal infections rises the closer one is to the equator (14).

Corneal abrasion or significant trauma from any type of plant or organic material are the most common predisposing factors (16). Other risk factors include immunocompromise (including exposure to local or systemic corticosteroids), diabetes, HIV infection (17), impaired tearing, incomplete eyelid closure and poor hygiene practice in those who use contact lenses. Seasonal variations in incidence have also been described (8). Increasing rates have been described in the UK (18). Children are often affected (19).

There is limited specific annual incidence data for fungal keratitis as most estimates relate to microbial keratitis of all causes. In tropical regions approximately half of of all microbial keratitis cases (all causes) are widely reported to be caused by fungal infections. The annual incidence of microbial keratitis varies with geographical location:

- USA: incidence of microbial keratitis (all causes) is 11 cases / 100,000 / year (20);

- UK: incidence of fungal keratitis was estimated at 0.034 cases / 100,0000 / year in 2003-05 (21);
- Germany: incidence of fungal keratitis was estimated at 0.04 cases / 100,0000 / year in 2003-05 (22);
- Denmark: incidence of fungal keratitis was documented at 0.05 cases / 100,0000 / year in 2014 (23);
- Hong-Kong: incidence of microbial keratitis (all causes) was estimated at 6.3 cases / 100,000 / year (24);
- Mexico: incidence of fungal keratitis was estimated at 10.4 cases / 100,0000 / year in 2015 (25);
- Vietnam: incidence of fungal keratitis was estimated at 7 cases / 100,0000 / year in 2015 (26);
- India: incidence of microbial keratitis (all causes) 113 cases / 100,000 / year (27);
- Bhutan: incidence of microbial keratitis (all causes) 339 cases / 100,000 / year (8);
- Myanmar: incidence of microbial keratitis (all causes) 710 cases / 100,000 / year (8);
- Nepal: incidence of microbial keratitis (all causes) 73 cases / 100,000 /year 8 (28, 29).

It is estimated that 12 million cases of microbial keratitis occur every year in South East Asia but it is unknown what proportion of cases ends up with visual loss or blindness. A statistically significant correlation has been found between Gross National Income (GNI) and aetiology of microbial keratitis. Fungal keratitis is associated with low GNI countries (30). In 2002, a government report from India estimated that keratitis accounted for 9% of cases of blindness in India (31). In Ugandan children with visual impairment, visual loss after corneal ulceration was responsible for nearly 25% of cases (32).

The annual incidence of microbial keratitis in contact lens wearers varies: 1.2-1,304 /10,000, depending on the type of lens, overnight use and the quality of lens care (33, 34). The proportion of microbial keratitis cases caused by fungi in contact lens wearers varies from 0.33% to 50% (30). An international outbreak of *Fusarium* keratitis in contact lens users occurred in 2004-2006, related to loss of disinfecting capability of the ReNu contact lens solution, now withdrawn (35, 36). Young adults are predominantly at risk, with men more often affected than women. In one series nearly 4% of cases were found in children (37). The rate of HIV infection in those presenting with fungal keratitis in Tanzania was twice the documented rate in the adult population (17), confirmed by other workers (35).

9.2. Assessment of current use

9.2.1. Clinical use and recommended regimens for Natamycin ophthalmic suspension

- Fungal Keratitis. Natamycin 5% eye drops used hourly initially (day and night). Eye examination every 2 days until the ulcer starts improving. The frequency of treatment is adjusted according to the clinical response. Typically drops are continued at least 3 hourly for at least 2 weeks after healing of the ulcer. Prolonged treatment courses lasting several weeks are usually necessary.

9.2.2. Use in Special Populations

Disadvantaged populations

Globally the major burden of fungal keratitis falls on rural populations in low and middle income countries, particularly those in tropical regions. Minor injuries may not receive timely prophylaxis and may additionally be treated with traditional medication containing vegetable matter. Delay in diagnosis and treatment are major determinants of a poor clinical outcomes – leading to sight loss. This is particularly an issue where the primary health care (including primary eye care) and referral systems are weak. The widespread lack of appropriate treatment for fungal keratitis is a major barrier in many countries. Much of this sight loss is avoidable if known public health measures are applied effectively (8).

Children

- Similar indication and treatment as in adults

9.3. Target populations

- Patients of any age suspected of having fungal keratitis either with clinical features suggestive of the condition and/or microbiological confirmation.

9.4. Likely impact of treatment of the disease

Responses to topical antifungal therapy are reasonable, with 75% of corneas not severely affected and 60% of those severely affected being cured by topical 5% natamycin (38). Advanced disease on presentation is associated with worse outcomes (17).

10. Review of benefits: summary of comparative effectiveness in a variety of clinical settings

10.1. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Literature search: In this systematic review, a literature search was done in October 2016 using the following search terms: (Fungal Corneal Ulcer OR Fungal Keratitis OR Fungal Corneal abscess OR Fungal Infective Keratitis OR Fungal Corneal abscess OR fungal corneal abscess OR Mycotic keratitis OR Mycotic corneal ulcer) AND (Management OR Treatment) and in using the database search, the terms were: fungal eye infection/co, di, dm, dt, pc, rt, si, su, th [Complication, Diagnosis, Disease Management, Drug Therapy, Prevention, Radiotherapy, Side Effect, Surgery, keratomycosis/di, dm, dr, dt, rh, si, su, th [Diagnosis, Disease Management, Drug Resistance, Drug Therapy, Rehabilitation, Side Effect, Surgery, Therapy. This search was executed in PubMed, Google scholar, Embase, Global Health, Clinical Trials.Gov, Ethos and IndMed. Manual searches were also conducted using reference lists of some of the retrieved study articles.

This search yielded 3774 references. After removing duplicates and excluding studies that were not reporting treatment of fungal keratitis, we retained 283 studies which were reviewed in detail. For this summary of the published data we only include randomized controlled trials involving topical treatment with Natamycin for fungal keratitis. We identified seven RCTs in which Natamycin was compared to alternative treatments. These are summarised in Table 1.

Table 2 shows the more relevant aspects included in the Guidelines for the Management of Corneal Ulcer at Primary, Secondary & Tertiary Care health facilities in the South-East Asia Region, World Health Organization Regional Office for South-East Asia, 2004 (8).

10.2. Summary of available data

(appraisal of quality, outcome measures, summary of results)

Table 1 and 2 show a summary of the available data

The usual primary outcome of trials is best corrected spectacle visual acuity (BCSVA) at 3 months, with a healed ulcer early in therapy another commonly used endpoint. The widely used LogMAR chart comprises rows of letters which are then scored to assess visual acuity. The WHO established criteria for visual using the LogMAR scale and blindness is defined as a best-corrected visual acuity worse than 1.3 LogMAR. Low vision is defined as >1.3 LogMAR in the better eye and <0.5 LogMAR in the worse eye.

Overall, there are three trials that have compared topical Natamycin 5% to topical Voriconazole 1%. A meta-analysis of these performed in a recent Cochrane review suggests that: **"There is evidence that natamycin is more effective than voriconazole in the treatment of fungal ulcers"**(39). The largest of these three studies, referred to as MUTT1, found quite a substantial benefit from Natamycin over voriconazole, particularly for *Fusarium spp.* infections, which are often the majority (4). It was felt by the reviewers that there was insufficient evidence to reach any other firm conclusions in relation to the other comparisons that had been performed.

Table 1. Natamycin clinical trials for fungal keratitis.

Chlorhexidine gluconate (CHX) vs Natamycin (NATA)			
Reference	**Design / Intervention**	**Results**	**Comment**
(6)	Prospective RCT with four arms: (1) g-Natamycin 5% (2) g-chlorhexidine 0.05% (3) g-chlorhexidine 0.1% (4) g-chlorhexidine 0.2% Outcome measures: • Favourable response at 5 days • Healed ulcer at 21 days • Toxicity	N=60 If the data from all three CHX arms are combined the following results are obtained (40): 1) Favourable response at 5 days RR 0.76, 95%CI: 0.44 - 1.33 2) Healed ulcer at 21 days RR 0.75, 95%CI: 0.38 – 1.49 (RR<1 Favours CHX) No toxicity reported Fungus speciated in 41 cases: 22 *Fusarium*, 10 *Aspergillus*, 3 *Curvularia*, 6 other.	Initial pilot trial to compare various concentrations of CHX. The sample size is therefore small and insufficient for a comparison with NATA 5%. Masking examiner to NATA is problematic as can leave a white precipitate on ocular surface. The CHX 0.2% was associated with a favourable response at 5 days in all (6/6) cases and most (5/6) had healed by day 21. The NATA 5% group responded less well at 5 (7/14, 50%) and 21 (7/14, 50%) days.
(7)	RCT Arms: (1) g-Natamycin 2.5% (2) g-chlorhexidine 0.2% Outcome measures: • Favourable response at 5 days • Healed ulcer at 21 days • Toxicity	N=71 1) Favourable response at 5 days RR 0.24, 95%CI: 0.09 – 0.63 2) Healed ulcer at 21 days RR 0.78, 95%CI: 0.54 – 1.14 (RR<1 Favours CHX) One patient receiving CHX had temporary punctate epitheliopathy Fungus speciated in 59 cases: 22 *Fusarium*, 22 *Aspergillus*, 5 *Curvularia*, 10 other.	This study used NATA of half the usual strength (2.5% instead of 5%). Masking examiner to NATA is problematic as can leave a white precipitate on ocular surface. A combined analysis (40) of these two trial of CHX vs NATA suggests that CHX has significantly more favourable responses to NATA at 5 days: RR 0.46, 0.28 – 0.77. However, at day 21 there was no significant difference in the proportions of healed ulcers: RR 0.77, 95%CI: 0.55 – 1.08.

Econazole vs Natamycin			
Reference	**Design / Intervention**	**Results**	**Comment**
(5)	RCT Arms: (1) g-Natamycin 5% (2) g-Econazole 2% Outcome measure: • "Success" – healed or healing ulcer at the final visit	N=116 No difference between the two treatments: RR 0.99, 95%CI: 0.8 – 1.21 Fungus speciated in 112 cases: 64 *Fusarium*, 30 *Aspergillus*, 6 *Curvularia*, 12 other.	Masking examiner to NATA is problematic as can leave a white precipitate on ocular surface.

Voriconazole (VOR) vs Natamycin (NATA)			
Reference	**Design / Intervention**	**Results**	**Comment**
(2)	RCT Arms (1) g-Natamycin 5% with scraping (2) g-Natamycin 5% no scraping (3) g-Voriconazole 1% with scraping (4) g-Voriconazole no scraping Scrapping was done at baseline for all cases for microbiology and then repeated in the scraping arms at one and two weeks. Outcome measures: • Best corrected spectacle visual acuity (BCSVA) at 3 months (primary outcome) • Scar size • Perforations	N=120 After adjusting for scraping, Voriconazole had a non-significant trend towards a slightly better visual acuity measured in logMAR units at 3 months: 0.98 logMAR better, 95%CI: -0.28 to 0.83, p=0.29. Eyes that had repeated scraping showed a non-significant trend towards having a worse visual acuity at 3 months: 0.71 logMAR worse, 95%CI: -0.007 to 0.35, p=0.06 No difference in the time to re-epithelialization between the NATA and VOR groups, p=61 Fungus speciated in 102 cases: 44 *Fusarium*, 19 *Aspergillus*, 39 other.	Masking examiner to NATA is problematic as can leave a white precipitate on ocular surface.

(3)	RCT Arms (1) g-Natamycin 5% (2) g-Voriconazole 1% Outcome measure: • Time to healing of ulcer • Visual Acuity	N=30 Non-significant difference in the time to resolution, which was shorter in the NATA vs the VOR groups: 24 vs 27 days (p>0.05) Fungus speciated in 25 cases: 3 *Fusarium*, 12 *Aspergillus*, 9 *Curvularia*, 1 other.	Masking examiner to NATA is problematic as can leave a white precipitate on ocular surface.
(4)	RCT Arms (1) g-Natamycin 5% (NATA) (2) g-Voriconazole 1% (VOR) Drops were applied hourly until re-epithelialisation. Then QID for at least 3 further weeks. Outcome measures: • Best corrected spectacle visual acuity (BCSVA) at 3 months (primary outcome) • Culture positivity after 5 days of treatment • Time to healing • Scar size • Perforations	N=323 Primary Outcome: Best corrected spectacle visual acuity measured in logMAR units at 3 months: VOR 1.8 lines poorer , p=0.006 Secondary Outcomes: • logMAR BSCVA at 3 weeks: VOR 1.1 lines poorer, p=0.03 • Fusarium Cases Only: logMAR BSCVA at 3 months: VOR 4.1 lines poorer, p<0.001 • Day 6 re-culture positive: NATA 15% vs VOR 48%, p<0.001. • Re-epithelialization: faster in *Fusarium* cases with NATA: hazard ration 1.89, p=0.005 • Scar size: *Fusarium* cases had significantly smaller scars at 3 months if treated with NATA, -1.02mm, 95%CI: -1.46 to -0.58. • Perforations and /or Therapeutic Penetrating Keratoplasty: 18 NATA vs 34 VOR. All cases: OR 0.42, 95%CI: 0.22 – 0.80, p=0.009. Fusarium only: OR 0.06, 95%CI: 0.01 – 0.28, p<0.001. Fungus speciated in 255 cases: 128 *Fusarium*, 54 *Aspergillus*, 20 *Curvularia*, 56 other.	The arms were well balanced in terms of the demographic, baseline clinical signs and organisms cultured. Masking examiner to NATA is problematic as can leave a white precipitate on ocular surface.

g-Natamycin + g-Voriconazole vs. g-Natamycin + intrastromal Voriconazole			
Reference	**Design / Intervention**	**Results**	**Comment**
(41)	RCT Arms (1) g-Natamycin 5% + g-Voriconazole 1% (2) g-Natamycin 5% + intrastromal Voriconazole injection 50µg/0.1ml Outcome measures: • BCSVA at 3 months (primary) • Time to healing • Scar size • Perforations	N=40 BCSVA at 3 months was better in the topical Voriconazole group (p=0.008) (1) logMAR 1.29 (2) logMAR 1.69 Time to healing was a bit faster (NS) in the topical group: (1) 28.9 days vs. (2) 36.1 days (p=0.38). Scar size tended (NS) to be bigger in the intrastromal injection group (p=0.06): (1) 4.4mm vs. (2) 5.3mm. Perforations occurred in 1/20 topical vs. 4/20 intrastromal (NS).	

Table 2. Natamycin recommendations in guidelines

Reference	Methodology	Quality of evidence & Recommendation	Doses	Comments
(8)	The Regional Office commissioned a study in 1999 to prepare an epidemiological and microbiological profile of corneal ulcer in the Region. This study identified the magnitude of the problem, microbial pattern of infection, antibiotic/antifungal sensitivity of the microbes as well as modifiable risk factors. Subsequently, these findings were reviewed at an intercountry meeting on corneal blindness held in 2002. The participating countries recommended to WHO to develop definitive guidelines for the treatment of corneal ulcer suitable for use at different levels of health system. To respond to the above request, WHO entered into a contract with the Aravind Eye Care System (AECS) in Madurai, India, a WHO collaborating centre, for development of the guidelines. The first draft of the guidelines was prepared by Dr M Srinivasan and his colleagues based on the findings of the above cited study and review of the more recent literature. This draft was circulated among over 200 clinical and public health experts. Their inputs were incorporated in the revised draft which was reviewed by selected experts from six WHO collaborating centres and corneal experts across the globe.	No quality of evidence & recommendation	Natamycin 5% eye drops hourly. Eye examination every 2 days until the ulcer starts improving. Then continue drops at least 3 hourly for at least 2 weeks after healing of the ulcer	

11. Reviews of harms and toxicity: summary of evidence on safety

11.1. Estimate of total patient exposure to date

Topical natamycin has been used extensively for the treatment of fungal keratitis in South Asia, South-East Asia and North America. It has recently become the standard of care in the UK (Ref: Moorfields Eye Hospital Fungal Keratitis Protocol). It is less widely used in continental Europe or Africa where it is not readily available. It is likely that many tens of thousands of people have been treated with topical natamycin for fungal keratitis. Formal data not available.

11.2. Description of the adverse effects/reactions and estimates of their frequency

11.2.1. Adverse events

- Natamycin ophthalmic suspension 5% is contraindicated in individuals with a history of hypersensitivity to any of its components
- There have been no long-term studies done using natamycin in animals to evaluate carcinogenesis, mutagenesis, or impairment of fertility
- The following events have been identified during post-marketing use of natamycin in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to their seriousness, frequency of reporting, possible causal connection to natamycin or a combination of these factors include: allergic reaction, change in vision, chest pain, corneal opacity, dyspnoea, eye discomfort, eye oedema, eye hyperaemia, eye irritation, eye pain, foreign body sensation, paraesthesia, and tearing (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050514s009lbl.pd)
- Experience from carefully reported clinical trials indicate that these events are rare and that topical natamycin is generally well tolerated (42)

11.3. Identification of variation in safety that may relate to health systems and patient factors

There are no known ethnicity or gender specific toxicities.

12. Summary of available data on comparative costs and cost-effectiveness within the pharmacological class or therapeutic group

12.1. Range of costs of the proposed medicine

Natamycin is not available in Nepal, Ecuador, Chile or Madagascar. In the Philippines and Denmark, it can be specially imported. It is actively sold in India and Myanmar. There is some variation in the cost of topical Natamycin 5% by region. In Peru a single bottle of natamycin 5% is 470 peruvian soles (USD $140), in Indonesia it is Rp 50,000 (~USD$4) and in the UK it is £330 per bottle. This availability work is ongoing by GAFFI.

12.2. Resource use and comparative cost-effectiveness presented as range of cost per routine outcome

No data available.

13.Summary of regulatory status of the medicine

13.1. US Food and Drug Administration

- Natamycin ophthalmic suspension 5% is indicated for the treatment of fungal blepharitis, conjunctivitis, and keratitis caused by susceptible organisms including *Fusarium solani* keratitis.

14.Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopeia, European Pharmacopeia)

- https://www.drugs.com/mtm/natamycin-ophthalmic.html
- https://online.epocrates.com/drugs/2545/natamycin-ophthalmic

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