

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

Nystatin

**Nilstat
Nystatin Lederle Tropfen
Nystatin Lederle Filmtabletten
Nystatin Lederle Paste**

DK/W/0019/pdWS/001

Rapporteur:	Denmark
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Nilstat Nystatin Lederle Tropfen, 100,000 I.U./ml Nystatin Lederle Filmtabletten, 500,000 I.U. Nystatin Lederle Paste, 100,000 I.U./g
INN (or common name) of the active substance(s):	Nystatin
MAH (s):	Teofarma S.r.l. MEDA Pharma GmbH & Co. KG (MEDA)
Pharmaco-therapeutic group (ATC Code):	A01AB33 A07AA02 D01AA01
Pharmaceutical form(s) and strength(s):	Oral suspension, 100,000 I.U./ml Film coated tablets, 500,000 I.U. Cutaneous paste 100,000 I.U./g

I. EXECUTIVE SUMMARY

Nystatin has been in continuous use in children since the 1950's. Nystatin is non-absorbable and is used to treat and prevent candida infections of the mucosa and skin. Although the majority of studies examining the efficacy and safety of Nystatin are old and few new studies are available, the efficacy and very high safety of Nystatin for prophylaxis and treatment of oral candidiasis in children and neonates is well established, in addition several recent studies and systematic reviews have confirmed its efficacy in the prevention of fungal infections in low birth weight neonates.

No SmPC or PL changes are proposed by the MAHs.

Summary of outcome

- No change
- Change
- New study data: <section(s) xxxx, xxxx>
- New safety information: <section(s) xxxx, xxxx>
- Paediatric information clarified: section 4.2
- New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION¹

The MAH is requested to introduce the following definitions of age groups for the oral formulations as part of the next regulatory update of the SmPC and PIL:

4.2 Posology and method of administration

Oral candidiasis

- Neonates (from birth to 1 month)
- Infants (1 month to 2 years)
- Children (≥ 2 years) and adults

Intestinal candidiasis

Newborns and infants (1 month to 2 years)

¹ The recommendation from section V can be copied in this section.

III. INTRODUCTION

In accordance with Article 45 of the Regulation (EC), No 1901/2006, as amended on medicinal products for paediatric use, two MAH (Teofarma and MEDA) has submitted clinical expert statements regarding the paediatric use of nystatin. Teofarma produces Nilstat (Nystatin). 100.000 IU/ml oral solution and has provided a very short critical expert overview.

MEDA is responsible for “Nystatin Lederle Tropfen, 100.000 IU/ml, oral solution”, “Nystatin Lederle Filmtabletten, 500,000 I.U. film coated tablets” and “Nystatin Lederle Paste, 100.000 IU/g cutaneous paste” and has submitted a comprehensive and well written clinical expert statement.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Nilstat and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal products
- A copy of the MEDA produced clinical expert statement on paediatric studies of Nystatin from 2012 and the brief clinical expert statement from Teofarma.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Nystatin oral suspension, 100,000 I.U./ml.

Nystatin, film-coated tablets, 500,000 I.U.

Nystatin 100,000 I.U./ g, cutaneous paste

Nystatin was discovered in 1950 and has been used since 1954. The compound is a naturally occurring antibiotic isolated from the soil actinomycete, *Streptomyces noursei* and is a member of the polyene family of antifungal agents. It irreversibly binds to specific sterol components (ergosterol) of the fungal cell membrane. Nystatin has a much higher affinity to ergosterol, which forms the fungal cell membrane compared to cholesterol, which forms the animal cell membrane. Given in low concentration nystatin is fungistatic; in higher concentrations nystatin is fungicidal. Nystatin is active against most *Candida* species.

The oral bioavailability of nystatin is poor, and only minimal amounts of anti-fungal activity have been observed in blood after high oral doses. The oral route, as well as the topical route, is therefore considered safe for clinical use in children and adults, as systemic exposure is minimal.

Details of 4.1 and 4.2 in the two current SPCs from Teofarma and MEDA are shown below:

Teofarma

PHARMACEUTICAL FORM

Nystatin

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NILSTAT is an oral suspension containing 100.000 U. of nystatin/ml
Pack of 30 ml (with a graduated dropper).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prophylaxis and treatment of mycotic infections, in particular those induced by *Candida Albicans*: candidiasis of oral cavity and intestinal tract.

Nilstat oral suspension is indicated for treatment of candidiasis in the newborn.

4.2 Posology and method of administration

Oral candidiasis

- Neonates (from birth to 1 month): clinical studies of limited size in newborns, including preterm and babies of low weight at birth, indicate that 1 ml (100,000 U) four times daily is an effective regimen.
- Infants (1 month to 2 years): 2 ml (200,000 U) 4 times daily (1 ml for each side of the mouth)
- Children and adults: 4 – 6 ml (400,000 – 600,000 U) 4 times daily (half dose in each side of the mouth). It is recommended to keep the medication in contact with the affected areas as long as possible.

Intestinal candidiasis

Newborns and infants

1-2 ml four times daily administered with milk or other liquid.

If needed, the dose can be increased, even in the newborn. Treatment should be continued for at least 48 hours after clinical cure and/or normalisation of cultures to avoid a relapse.

MEDA (SPC, translated from German):

NAME OF THE MEDICINAL PRODUCT

Nystatin *Lederle* Tropfen, 100 000 I.U. / ml, oral suspension

Nystatin *Lederle* Filmtabletten, 500 000 I.U.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Nystatin

Nystatin *Lederle* Tropfen:

Each ml of oral suspension contains 100 000 I.U. of nystatin, equivalent to 20 mg of dry substance (Ph. Eur.)

Nystatin *Lederle* Filmtabletten:

Each film-coated tablet contains 500 000 I.U. of nystatin, equivalent to 100 mg of dry substance (Ph. Eur.) For a full list of excipients, see section 6.1.

Nystatin

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3. PHARMACEUTICAL FORMS

Nystatin Lederle Tropfen: Suspension for oral use and for use in the oral cavity

Nystatin Lederle Filmtabletten: Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nystatin Lederle Tropfen:

Infections in the mouth and the gastrointestinal tract caused by detected nystatin-sensitive yeast fungi (*Candida albicans*, *Candida (Torulopsis) glabrata* and others).

Nystatin Lederle Filmtabletten:

Infections in the gastrointestinal tract caused by detected nystatin-sensitive yeast fungi (*Candida albicans*, *Candida (Torulopsis) glabrata* and others).

4.2 Posology and method of administration

In general, frequency of use and dosage will depend on the severity/extent of disease and the patient's condition.

Posology

Nystatin Lederle Tropfen

Oral thrush in infants:

4–6 times daily 0.5–1 ml of oral suspension.

Oral thrush in children and adults:

4–6 times daily 1 ml of oral suspension.

Intestinal thrush in infants:

4 times daily 1–2 ml of oral suspension.

Nystatin Lederle Filmtabletten

The usual daily dose is:

3–4 times daily two film-coated tablets for 8 days, thereafter 3–4 times daily one film-coated tablet for another 8 days.

In patients with severely impaired defense response, higher dosages and more frequent use of Nystatin Lederle Tropfen and Nystatin Lederle Filmtabletten, respectively, may be required.

Since nystatin is practically not absorbed by the body due to its molecular size, oral administration is also a topical treatment.

As late as with maximum concentrations of approximately 8 million I.U. and above (equivalent to 16 film-coated tablets or 80 ml of oral suspension per single dose) a low and therapeutically ineffective serum concentration of nystatin becomes measurable.

Method of administration

Nystatin Lederle Tropfen

Shake the oral suspension before each use.

Oral thrush:

After the meals, the oral suspension should be dropped or sprayed into the mouth and should be kept in contact with the affected areas as long as possible before swallowing. It is important to wet the oral cavity completely. In infants, it is recommended to use a spatula in order to apply the medicine to the cheek pouches and labial pouch as well. Before this, any thrush patches should be wiped off using a swab.

Intestinal thrush in infants: Administer the oral suspension before the meals.

In the pack containing a pipette, the pipette is marked for dosing 0.5 ml and 1 ml, respectively, of oral suspension. In case of the packs containing a metered-dose pump, 2 pump actuations are equivalent of 1 ml.

Nystatin Lederle Filmtabletten

The film-coated tablets should be taken after the meals with sufficient liquid.

Nystatin Lederle Tropfen and Nystatin Lederle Filmtabletten

After the symptoms have disappeared, treatment should be continued for at least another two days, and a microbiological control test should be arranged for.

Even if the symptoms improve within a few days, treatment should not be interrupted. If local skin irritations are developed, a doctor should be consulted immediately. In cases where no therapeutic success occurs, a suitable microbiological test shall be carried out before any other treatment is considered.

IV.2 Clinical and Non-clinical aspects

1. Introduction

No new relevant non-clinical studies were identified by the applicants or the assessor.

Pharmacokinetics

Topic application

Absorption

The nystatin cutaneous paste is for topical use on infected skin areas and there is no indication of absorption across the skin resulting in systemic exposure to nystatin. This is in line with observations for other polyene antibiotics.

Nystatin is not absorbed across mucosal layers when applied topically. Thus systemic toxicity is not to be expected with topical preparations.

Distribution

As there is no penetration across the skin, the determination of standard pharmacokinetic evaluations of distribution would not be appropriate, as there would be no systemic exposure to nystatin.

Metabolism

No systematic investigations on the metabolism of nystatin have been performed. Essentially, based on long clinical experience with this compound this fact is considered to be of no clinical importance.

Excretion

As there is no penetration across the skin, the determination of standard pharmacokinetic elimination would not be appropriate, as there would be no systemic exposure to nystatin.

Oral application

Absorption

There is little to no oral absorption across the mucosa resulting in systemic exposure to nystatin. The limited oral absorption was insufficient to produce either a systemic chemotherapeutic effect or any toxicity. The serum concentrations of nystatin after oral administration are summarized below

Nystatin Dose [Units]	Plasma concentration [mcg/ml]	Reference
150,000 (neonates)	0	Hoppe, 1997
70,000- 1.4 m	1.7-2.0	Seneca, 1956
3-10 m	0-7	Drouhet, 1963
≥ 8 m	1-2.5	Hoppe, 1997
10 m	“some”	Kucers, 1976
15 m	2.0	Seneca, 1956

m: millions

There does not appear to be a dose response and for dose levels of 150,000 U to 15 million U, concentrations were very low ranging from 0-2.5mcg/ml in most cases; one report by Drouhet showed a higher level of 7.0 mcg/ml, but it was not dose related. These are very low concentrations and are barely therapeutic in terms of *Candida* minimum inhibitory concentrations (MICs). The interaction of nystatin and other polyenes with bile salts which leads to a reduction in activity seems to be a contributing factor to the poor oral bioavailability for these compounds.

Distribution

Systemic exposure after oral administration is minimal as evidenced by the very low recovery in urine of ≤ 1.0% at 24 h (dose not given), and the low and erratic concentrations in serum.

Metabolism

Nystatin concentrations persisted in saliva for approximately 2 hours after the start of oral dissolution of 2 nystatin pastilles (400,000 units). No systematic investigations on the metabolism of nystatin have been performed. Essentially, based on long clinical experience with this compound this fact is considered to be of no clinical importance.

Excretion

As would be expected for a poorly absorbed compound such as nystatin a higher proportion of dose would be in the faeces and this was the case in the study reported by Drouhet (1968); 32% of the nystatin dose was recovered in faeces compared with <1.0% in urine. The lack of total recovery of the dose may be due to the inherent instability of the compound. In *in vitro* studies, nystatin was shown to lose activity in plasma, blood and aqueous solutions (Hu, 1956).

Elimination half-life

As no or nearly no absorption after topical or oral application occur, no determination of elimination half-life was done.

Pharmacokinetic interactions

Synergy with other antibiotics such as tetracyclines has been observed (Holz, 1979) but the underlying mechanism is not clear although, it may in part be due to the increase in membrane permeability caused by polyenes (Aszalos, 1975).

The observations outlined above support the view that no deleterious effects would be expected if therapeutic agents were to be coadministered with nystatin.

OVERVIEW OF EFFICACY

Topical application

In a study by Bereston (1957), nystatin ointment (100,000 U/g, bid) proved effective in the treatment of cutaneous lesions of *Candida* in infants and children and there were 6 cures, 2 improvements and 3 failures (duration of treatment 1-8 weeks).

The efficacy of a topical cream formulation of nystatin (100,000 U/g) was investigated in a double blind clinical trial in 50 infants (6 days – 20 months old) and clinical conditions included diaper rash, intertrigo and paronychia (Alban, 1972). Twenty-five patients received the antibiotic and 25 the placebo. They were randomised in terms of age and sex and there were no significant differences between the groups. All patients had positive cultures for *C. albicans* before treatment. Patients received either qid or tid dosage and the average length of therapy was 5.7 and 6.3 days respectively. On the 5th day, 18 of the placebo patients and 4 of the nystatin group were changed to a known preparation of nystatin. Overall the clinical response in the dose group was significantly better than in the placebo only ($p=0.001$). Cultures were taken at intervals and at the end of therapy – 35% were positive in the nystatin group compared with 84% (18/25) in the placebo. Of the patients in the placebo group who changed to a known preparation of nystatin, 14 were negative, 3 remained positive and there was no culture for 1. Therefore overall, 78% evidenced a clearing of the initial pathogen (Alban, 1972). There were no side effects in either group.

Kozinn (1975) treated 37 cases of cutaneous candidiasis in newborn infants and young children – the actual doses were not stated. These were either early or advanced candidiasis. The early infections occurred in new-borns or in infants younger than 2 weeks and the majority of cases occurred concomitantly with oral thrush. There were also other sites of infection. The advanced type occurred in infants between 3 weeks and 2 years of age and the infections extended over the lower abdomen, upper thighs and in the inguinal area. The children had been infected for about 2 weeks before treatment and *C. albicans* was isolated from the lesions. A 2% ointment was used in a base consisting of 95% liquid petrolatum and 5% polyethylene. All of the patients with the early infections improved after only 24h of treatment. After treatment periods ranging from 2-8 days, all (9/9) were cured. In the advanced cases, 10/14 were cured (average length of therapy 17.8 days) and 1/14 improved – there were 3 failures. On the whole, nystatin proved superior to amphotericin B (84% cures vs. 80%) and the cure rates were similar to those observed in previous studies.

Munz (1982) compared the efficacy of topical nystatin treatment with a combined oral and topical nystatin treatment in 37 infants with candidal diaper dermatitis. Group 1 (16 patients) received topical and oral nystatin, group 2 (21 patients) topical nystatin and oral placebo. All 37 infants whose initial skin cultures grew *C. albicans* had improved in at least one of the three clinical criteria after 10 days of therapy. There was no difference in the clinical course between groups 1 and 2. Although the area of rash appeared to be less in group 2 patients after 10 days of treatment, the difference was not significant. Treatment for longer than 10 days was necessary for 11 children (65%) in group 1 and 9 children (43%) in group 2. About one third of the children in both groups had a clinical recurrence within the following year.

These results suggest that topical nystatin alone is as effective as combined oral and topical therapy.

[De Wet \(1999\)](#) assessed the efficacy and clinical outcome of a standard nystatin cream (100,000 U/g) and 2% of the antibacterial agent mupirocin (in a polyethylene glycole base in diaper candidosis. It was a prospective randomised comparative study. The susceptibility of 20 clinical isolates of *Candida albicans* to 2% mupirocin, nystatin, and five additional antifungal agents was evaluated using the Nathan agar-well diffusion assay. The MIC of mupirocin was determined using a tube dilution method. Twenty patients (mean age: 12 months; range: 1 month to 4 years) with moderate to severe diaper dermatitis received mupirocin ointment or nystatin cream applied to the infected area every 8 h or after every diaper change for a period of 7 days. Microscopic examinations of skin scrapings and mycologic and microbiological cultures were performed before treatment and daily for 7 days, and progress was clinically assessed. *C. albicans* isolates were susceptible to nystatin and mupirocin. There were differences in healing rates between the groups and some advantage was shown for mupirocin, presumably because the infections were polymicrobial containing both fungi and bacteria. *Candida* was however successfully cleared within 5 days (mean 2.8 days) in the nystatin group and within 2-6 days (mean 2.6) in the group receiving mupirocin.

[Hoeger \(2010\)](#) included 96 infants with diaper dermatitis in a multi-centre, controlled, randomized, evaluator-blinded phase IV trial for treatment with pastes containing either clotrimazole (n=45) or nystatin (n=46) twice daily for 14 days. Symptoms improved markedly with both pastes. Decrease in symptom score was slightly better with clotrimazole compared with nystatin (n=46). Microbiological cure rate was 100% for both agents. Both treatments were safe and well-tolerated.

[Howell \(2009\)](#) compared the incidence of fungal infection in babies in neonatal units which do and do not give antifungal prophylaxis using oral nystatin. Therefore he conducted a prospective, multi-centre surveillance study from 1993 to 2006 of invasive fungal infection in babies < 1500 g birth weight in neonatal units. The incidence of invasive fungal infections was 0.54% for babies with selective or universal oral nystatin prophylaxis and 1.23% for babies without prophylaxis. This showed that antifungal prophylaxis with oral nystatin was associated with a significantly lower incidence of fungal infection compared with no prophylaxis.

[Ward \(2000\)](#) examined encounters from the National Ambulatory Medical Care Survey in US between 1990 and 1997 for visits in which diaper dermatitis was diagnosed in children. Nystatin was the leading treatment agent prescribed (27% of visits), followed by clotrimazole (16%), a combination product of nystatin and triamcinolone (16%), hydrocortisone (8%), and a combination product of clotrimazole and betamethasone dipropionate (6%).

Oral application

In a clinical trial in 55 infants (<1-12 months) suffering from oral thrush, 29 were treated with a nystatin suspension (100,000 U/ml) 4 times daily directly into the mouth immediately after the feeds and 26 were treated with 1% solution of Gentian Violet ([Graham, 1959](#)). On day 7, nystatin cleared the infection in 22/29 patients, whereas only 8/26 were cleared in the Gentian violet group. On day 14 28/29 and 16/26 respectively were cleared. There was a relapse in 1 patient receiving nystatin and 3 receiving the dye.

[Doxiadus \(1959\)](#) instilled oral nystatin at a lower dose (4 drops of a 100,000 U/ml suspension – equivalent to approximately 20,000 U into the mouths of 28 neonates and compared the

outcome with results obtained after administration of sodium bicarbonate (36 patients). Nystatin again proved to be highly and rapidly effective compared with sodium bicarbonate and at 10 days all babies were cleared of infection compared with 13/36 patients. Nystatin was non-irritating, non-toxic and non-allergic and no case was resistant to nystatin. These studies support the earlier reports of [Huang \(1955/56\)](#) in which all cases of oral thrush in infants (premature and normal) responded to local treatment (4 times daily) of various oral formulations of nystatin. There were no adverse effects.

A prospective open randomized multicentre study in Germany involving 12 paediatricians in private practice compared two commercial nystatin gels (a) contained 250,000 U/g and a single dose was 1g and (b) contained 100,000 U/g and the single dose was 50,000 U) with miconazole oral gel (20 mg miconazole/g, a 25 mg single dose) in 95 infants with oral thrush ([Hoppe, 1996](#)). All medications were given 4 times a day and the duration of therapy depended upon the quantity of compounds within the tubes; 10 days for nystatin (a), 15 day for nystatin (b) and 8 days for miconazole. Oral and rectal swabs were taken on days 0 and 14. On day 14, clinical cure was observed in 85.1% of infants treated with miconazole compared with 42.8% and 48.5% of infants treated with the nystatin gels (a and b respectively). There were clinical relapses in the nystatin groups and the overall oral mycologic cure rate was similar for nystatin gel (a) and miconazole (20% and 30%) and both were significantly ($p=0.005$ and 0.03) higher than for the nystatin (b) gel (3%). This may have been related to the higher single dose that was used for this formulation.

[Hoppe \(1997\)](#) undertook further comparisons with the miconazole gel (20mg/g – single dose 25 mg), but in these studies a nystatin suspension was used (100,000 U of nystatin as suspension four times daily after meals). Twenty-six paediatricians enrolled 227 immunocompetent infants with signs of oropharyngeal thrush. Clinical cure by Day 5 of treatment was demonstrated in 84.7% of the 98 subjects in the miconazole group and 21.2% of the 85 subjects in the nystatin group ($p=0.0001$) and by Day 12, 99.0% of the miconazole group and 54.1% of the nystatin group were clinically cured ($p=0.0001$). The oral yeast eradication rate on Day 5 was 54.1% with miconazole and 8.2% with nystatin ($p=0.0001$). The numbers of relapses and side effects were similar for the two agents.

[Flynn \(1995\)](#) found nystatin gel to be less effective than fluconazole in the treatment of oropharyngeal thrush. This was a multicenter, randomised, observer-masked trial. Thirty-two centers participated and they included hospitals and ambulatory care clinics. 182 immunocompromised infants and children (5 months to 14 years) with signs of oral thrush and presence of yeasts were enrolled and they were randomly assigned to receive a single daily dose of fluconazole suspension, 2 to 3 mg/kg per day, or nystatin suspension 400,000 U four times daily for 14 days; 159 patients, who had culture confirmation of thrush and received at least 7 days of study drug, were included in the study. Clinical cure was demonstrated in 91% of the subjects in the fluconazole group and 51% of the subjects in the nystatin group ($p<0.001$), and eradication of the organism cultured at entry occurred in 76% and 11% ($p<0.001$), respectively. Clinical relapse rates after the completion of study drug were however similar in both groups at 2 weeks (18% and 24% for fluconazole and nystatin, respectively) and 1 month (28% and 27%, respectively).

[Groll \(1997\)](#) conducted an open, prospective, randomized pilot study to assess the efficacy and safety of oral fluconazole 3 mg/kg once daily compared with oral nystatin 50,000 units/kg/day in four divided doses in preventing candida infections in 50 children undergoing remission induction or consolidation therapy for cancer. In 21 of 25 fluconazole-treated and 20 of 25 nystatin-treated patients the overall outcome of prophylaxis was clearly successful. Nystatin was as safe and effective as fluconazole in controlling yeast colonization and in preventing superficial and invasive candida infections.

Efficacy of Nystatin for the prevention of fungal infection in newborn/neonates

Invasive fungal infection is an important cause of mortality and morbidity in very preterm (< 32 weeks gestation) or very low birth weight (VLBW) infants.

Two recent reviews of Nystatin for the prevention of neonatal fungal infections have been published and are referenced by the MAH Teofarma. Below, key findings from these reviews are summarized and discussed:

Blyth CC, Barzi F, Hale K, Isaacs D: Chemoprophylaxis of neonatal fungal infections in very low birthweight infants: efficacy and safety of fluconazole and nystatin. J Paediatr Child Health 2012, 48:846-851.

Description

In this systematic review of randomised controlled trials, Blyth and coworkers reviewed the use of antifungal chemoprophylaxis to prevent neonatal invasive fungal infections (IFI) in very low birth weight infants (VLBW<1500 g) [1].

Methods

Nine trials, published between 1988 and 2012, were identified (2029 infants), with six comparing fluconazole with placebo/no treatment (840 infants), three comparing nystatin with placebo/no treatment (1200 infants) and two comparing fluconazole and nystatin (257 infants).

Findings

Prophylactic fluconazole reduced the incidence of invasive fungal infections (IFI) in VLBW infants to 5.1% compared with 16.0% in infants receiving placebo, relative risk (RR) = 0.36 (95% confidence interval 0.15–0.89). The mortality was 10.9% and 16.7%, respectively (RR 0.76, 0.54–1.08). Oral nystatin reduced the incidence of IFI in VLBW infants to 5.3% compared with 28.0% in infants receiving placebo (RR 0.16, 0.11–0.23). Mortality was 7.5% with nystatin and 10.9% with placebo (RR 0.86, 0.59–1.26). The incidence of IFI in studies comparing fluconazole and nystatin was 3.6% and 8.0%, respectively (RR 0.54, 0.19–1.56), and mortality was not significantly different: 4.6% versus 9.8% (RR 0.43, 0–4.31).

There was no significant toxicity reported from oral nystatin in the studies reviewed and no babies were withdrawn from the studies because of adverse events.

In conclusion this meta-analysis suggests that oral nystatin is extremely effective in preventing IFI.

Chicella MF, Woodruff ED, Desai MM: A review of Candida prophylaxis in the neonatal intensive care population. J Pediatr Pharmacol Ther 2011, 16:237-245.

Description

Review of the efficacy and safety of antifungal prophylaxis in the neonatal intensive care setting [4].

Methods

English-language literature was accessed using MEDLINE (January 1988– December 2010). Literature was limited to studies focusing on patient birth to 6 months of age. Abstracts and original research articles were included. Preference was given to published controlled trials. Articles providing descriptions of the safety and effectiveness of antifungal prophylaxis in neonatal intensive care patients were also used in this review.

Findings

Twenty-two studies evaluated the impact of antifungal prophylaxis on *Candida* colonization or invasive infections in the Neonatal Intensive Care Unit (NICU). The two antifungal agents most commonly studied were nystatin and fluconazole. All of the nystatin studies used standard oral candidiasis dosing, 100,000 units (1 mL) of nystatin per dose. All of the nystatin studies demonstrated that nystatin is effective at reducing fungal colonization and invasive fungal infections. None of the studies included reported adverse drug reactions associated with nystatin use. All of the studies designed to evaluate the impact of fluconazole prophylaxis on fungal colonization demonstrated a reduction in the incidence of fungal colonization with fluconazole prophylaxis. A total of 12 of 16 studies that evaluated the impact of fluconazole prophylaxis on the incidence of invasive fungal infections demonstrated a reduction in invasive fungal infections with fluconazole prophylaxis. Two studies found no difference between fluconazole and nystatin when used for prophylaxis.

Summary, use in neonates

In addition to these studies, a Cochrane systematic review found that oral/topical non-absorbed antifungal prophylaxis with nystatin was associated with a statistically significant reduction in the incidence of invasive fungal infection as compared with placebo or no drug. A statistically significant effect on mortality was not found (Austin, 2009). However long-term outcomes were not assessed by any of the trials.

A large trial shows that oral nystatin prophylaxis significantly reduced the invasive candidiasis (in extremely low-birth weight (ELBW) and very low-birth weight (VLBW) infants (Ozturk, 2006).

Oral nystatin, which is non-absorbable, acts by reducing fungal colonisation of the gastrointestinal tract. It has not been reported to be associated with adverse events in neonates. In older children and adults, gastrointestinal symptoms including nausea and vomiting can occasionally occur, particularly when high doses are used for long periods. In addition to the Randomised Clinical Trial (RCT) evidence presented above, two observational studies support the efficacy of prophylactic nystatin. A large observational study from Australia and New Zealand compared the incidence of IFIs in neonatal units according to their use of routine nystatin prophylaxis. The incidence of IFI in units using no prophylaxis was 1.23% compared with 0.54% in units using universal or selective nystatin prophylaxis ($P < 0.0001$)[2] Although the study was not randomised, the large population (14 778 babies < 1500 g) and the size of the effect suggest that the effect is unlikely to be due to chance. Furthermore, the data suggest that prophylactic oral nystatin prevents neonatal fungal infections even when the incidence is low. Additionally, a single-centre sequential study from the UK found that the introduction of nystatin was associated with a fall in incidence in infants < 1500 g from 5.5 to 2.5% ($P = 0.012$)[3]. The dose of nystatin used in the randomised controlled trials is 100 000 units in 1 mL 8 hourly. It is usually started at the same time as oral feeds. Although there is no strong evidence for duration of nystatin prophylaxis, most neonatal units give it during the maximum risk period, which is until the infant no longer has a central line or endotracheal tube in place. Although most oral species of *Candida* remain susceptible to azoles, indiscriminate use of such drugs may lead to the spread of *C. krusei* and *C. glabrata*, intrinsically resistant to and dose-dependently sensitive to azoles,

respectively. In contrast, primary resistance to polyenes among *Candida* species is limited to *Candida lusitanae* and to some strains of *Candida guilliermondii*, and resistance seldom develops during treatment

Safety

Background

Polyene antibiotics can be cytotoxic and intravenous administration to animals has led to haemolytic anaemia, renal damage and subsequent death. Nystatin has also been shown to reduce the lysozyme activity of rat serum and partially to inhibit platelet aggregation (Hammond 1977). The adverse effects observed after systemic exposure to polyenes are probably in part due to interaction of nystatin and other polyenes with host cell membranes containing cholesterol. Because of the potential for high parenteral toxicity, the use of Polyene nystatin has been restricted to topical, inhalation or gastro-intestinal therapy (Hammond, 1977; Holz 1979). As an oral and topical agent, nystatin is very well tolerated.

There are virtually no side effects related to the topical use of nystatin. The drug does not cause irritation or allergic reactions when applied to the skin or mucosal membranes. In the early studies of Wright (1957) a variety of formulations were used for topical therapy of both cutaneous and vaginal infections in 108 male and female patients, and at no instance were there reports of allergic contact dermatitis or primary irritation.

Clinically nystatin topical is considered to be virtually non-toxic and non-sensitising and is well tolerated by all age groups even after prolonged dosing (Berkowitz, 1985). Topical cream and topical ointments together with the ointment and cream bases and nystatin powder were tested in animals for irritancy and also possible toxicity after oral administration (Yuda, 1970 a&b, 1972). No effects were observed and this would support the lack of significant adverse effects seen clinically.

Nystatin is generally considered not to be sensitizing (Berkowitz, 1985). However Garty (1991) reported one case of Stevens-Johnson syndrome in a 14-month old girl treated with an oral suspension of nystatin for oral thrush. There was increased severity of the reaction with each exposure to nystatin over a period of time, which implied a sensitizing action. Allergic contact dermatitis is rare and the author quoted only 2 other cases. Hammond (1977) reported three more cases, but overall this is a rare phenomenon.

Oral application

As early as 1957 it was found that nystatin could be administered either orally or locally to man with no adverse reactions. Transient nausea has been observed after oral doses of 500,000 U tid and qid, but others observed no adverse effects after oral dosing for up to 3 months (Florey, 1960). Side effects including nausea, diarrhoea and vomiting continue to be observed (Alvarez 1998), but as earlier studies only infrequently. Allergic dermatitis can occur, but it is rare (Rosenberger 1998).

Typical effects in patients of all age groups (Flynn, 1995) are gastrointestinal but usually not severe enough to withdraw from treatment.

5.2 Post-marketing experience/PSUR

TEOFARMA

No serious or medically significant non serious adverse reaction occurring in children was collected by Teofarma during post-marketing experience since it became MAH of Nilstat (December 2002).

MEDA

Detailed information concerning the post-marketing experience is summarised in the 1st PSUR. As Nystatin Lederle cutaneous paste and Nystatin Lederle oral suspension are authorized for paediatric use it also covers paediatric data. During the reporting period there were no urgent safety restrictions or other relevant regulatory safety actions.

Assessor's conclusion on safety

The safety of Nystatin oral suspension and paste is excellent.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Nystatin has an excellent and long track record of efficacy and safety for the prevention and treatment of candidiasis in the newborn and in children, which has recently been confirmed in systematic reviews. Although the efficacy of nystatin is inferior to azoles such as fluconazole or miconazole for treatment of candidiasis, particularly in immunosuppressed patients, the low cost, absence of side-effects and drug interactions together with efficacy against several candida strains with reduced azole susceptibility (such as *C.glabrata* and *C.tropicalis*) makes this drug an important part of the armamentarium against candida in neonates and children. Overall this review, as well as extensive and long term clinical experience, confirm the excellent safety of this non-absorbable drug and clearly support the continued use of nystatin in children and neonates.

Recommendation

The MAH is requested to introduce the following definitions of age groups for the oral formulations as part of the next regulatory update of the SmPC and PIL:

4.2 Posology and method of administration

Oral candidiasis

- Neonates (from birth to 1 month)
- Infants (1 month to 2 years)
- Children (\geq 2 years) and adults

Intestinal candidiasis

Newborns and infants (1 month to 2 years)

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMA

Teofarma S.r.l.

NILSTAT, 100,000 I.U./ml, oral suspension, drops

MEDA Pharma GmbH & Co. KG

Nystatin *Lederle* Tropfen, 100,000 I.U./ml, oral suspension

Nystatin *Lederle* Filmtabletten, 500,000 I.U., film coated tablets

Nystatin *Lederle* Paste, 100,000 I.U./g, cutaneous paste