Topical paromomycin with or without gentamicin for cutaneous leishmaniasis.


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Topical Paromomycin with or without Gentamicin for Cutaneous Leishmaniasis


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BACKGROUND

There is a need for a simple and efficacious treatment for cutaneous leishmaniasis with an acceptable side-effect profile.

METHODS

We conducted a randomized, vehicle-controlled phase 3 trial of topical treatments containing 15% paromomycin, with and without 0.5% gentamicin, for cutaneous leishmaniasis caused by Leishmania major in Tunisia. We randomly assigned 375 patients with one to five ulcerative lesions from cutaneous leishmaniasis to receive a cream containing 15% paromomycin–0.5% gentamicin (called WR 279,396), 15% paromomycin alone, or vehicle control (with the same base as the other two creams but containing neither paromomycin nor gentamicin). Each lesion was treated once daily for 20 days. The primary end point was the cure of the index lesion. Cure was defined as at least 50% reduction in the size of the index lesion by 42 days, complete reepithelialization by 98 days, and absence of relapse by the end of the trial (168 days). Any withdrawal from the trial was considered a treatment failure.

RESULTS

The rate of cure of the index lesion was 81% (95% confidence interval [CI], 73 to 87) for paromomycin–gentamicin, 82% (95% CI, 74 to 87) for paromomycin alone, and 58% (95% CI, 50 to 67) for vehicle control (P<0.001 for each treatment group vs. the vehicle-control group). Cure of the index lesion was accompanied by cure of all other lesions except in five patients, one in each of the paromomycin groups and three in the vehicle-control group. Mild-to-moderate application-site reactions were more frequent in the paromomycin groups than in the vehicle-control group.

CONCLUSIONS

This trial provides evidence of the efficacy of paromomycin–gentamicin and paromomycin alone for ulcerative L. major disease. (Funded by the Department of the Army; ClinicalTrials.gov number, NCT00606580.)
LEISHMANIA, A GENUS OF TRYpanosoma-
tid protozoa, is endemic in 98 countries or
territories worldwide, with infection trans-
mitted by the bite of a female sand fly. The esti-
mated yearly incidence of leishmaniasis infection is
1.5 million cases of cutaneous leishmaniasis and
500,000 cases of visceral leishmaniasis.1 Cutane-
ous leishmaniasis results from the parasitization of
skin macrophages and generally is manifested
as a papule that enlarges to a nodule that often
ulcerates during a period of 1 to 3 months. Dis-
verse leishmaniasis species cause cutaneous leish-
maniasis. There are at least five species, includ-
ing Leishmania major, on the Eurasian and African
continents and seven species in the Americas.2
Cutaneous leishmaniasis resolves without treat-
ment in a few months to several years, with the
period depending on the infecting species. For
L. major, there was resolution of single lesions by
45 days of follow-up in approximately 20 to 45%
of untreated patients in Tunisia or Iran, and ap-
proximately 70% had resolution of single lesions
by 105 days.2,3 Despite these findings, cutaneous
leishmaniasis can cause substantial morbidity
owing to the continued presence of a skin ulcer
and the psychological effect of disfigurement.4
The World Health Organization (WHO) disability
weight for cutaneous leishmaniasis is 0.023 (on a
scale of 0 to 1, with increasing values reflect-
ing more severe disease). This weight is greater
than that for malaria-induced anemia (0.012) and
similar to that for hookworm-induced anemia
(0.024).5

A variety of therapies for cutaneous leish-
maniasis exist and have been reviewed6–9 (19 in
a systematic review by González and colleagues
alone6). Clearly, there remains a need for a treat-
ment that is simple and efficacious with an ac-
ceptable side-effect profile.10,11

One nonsystemic treatment is the topical ap-
lication of paromomycin-containing creams. Par-
omomycin is an antibacterial aminoglycoside that
for unknown reasons also has efficacy against
leishmaniasis. The dose that is required to produce a
50% reduction in parasite load in in vitro samples
is generally between 1 and 40 µg per millili-
ter.12,13 The maximum serum concentration is
23 µg per milliliter after intramuscular adminis-
tration.13 Intramuscular paromomycin cured vis-
ceral leishmaniasis in 95% of patients in India15
but was less successful in those with cutaneous
leishmaniasis.16–18 To increase the amount of
paromomycin that is delivered to the skin and
parasites in these often-necrotic cutaneous les-
sions,19 El-On and colleagues20 created a formul-
lation containing 15% paromomycin in white soft
paraffin that also contained 12% methyl-
benzethonium chloride. This formulation was
more effective than no treatment for L. major
infection in Israel21 and more effective than vehi-
cle-control treatment for infection with L. mexi-
cana and L. braziliensis in Guatemala.22 However,
cost and “severe irritancy and intolerance” as-
associated with the use of 12% methylbenzetho-
nium chloride, as seen in up to 75% of pa-
tients,20 has resulted in the infrequent use of
this formulation.23–25 A cream containing 15%
paromomycin in white soft paraffin plus 10% urea
was sponsored by the WHO but was no
more effective than vehicle control against L. major
infection in Iran3 and Tunisia.2

We developed a cream containing 15% paro-
omycin sulfate plus 0.5% gentamicin sulfate in
a complex base (called WR 279,396) to aid drug
penetration. Gentamicin was included in the
formulation on the basis of efficacy studies in
mice showing that gentamicin augmented the
rate of cure and decreased the rate of relapse, as
compared with paromomycin alone, particularly
for species causing cutaneous leishmaniasis in
the Americas.26 Although gentamicin is not di-
rectly cytocidal to leishmania parasites, it may
attenuate them, facilitating immunologic mech-
nisms of eradication through helper T-cell im-
munity.27,28 In addition, combination products
may impart broad-range antibacterial activity
against secondary bacterial infections that could
otherwise delay wound healing, and such prod-
ucts may avert the development of resistance. In
a previous phase 2 study, WR 279,396 was more
effective than vehicle control against L. major
infection29 at the same site in Tunisia at which
the WHO formulation was ineffective.2 Here, we
report the results of our phase 3 randomized,
double-blind, vehicle-controlled, parallel-group
study in which we compared WR 279,396 (15%
paromomycin–0.5% gentamicin cream) with par-
omomycin alone (15% paromomycin cream) and
with vehicle-control cream against cutaneous
leishmaniasis caused by L. major in Tunisia.

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METHODS

STUDY DESIGN AND CONDUCT
From January 2008 through July 2011, we conducted the study at medical clinics in or near the area of Sidi Bouzid, Tunisia, in which the species is endemic. The protocol was approved by the ethics committee of the Institut Pasteur de Tunis and by the Human Research Protections Office, U.S. Army Medical Research and Materiel Command, and is available with the full text of this article at NEJM.org. The study was sponsored by the Office of the Surgeon General, Department of the Army, and is considered a phase 3 study by the Food and Drug Administration under Investigational New Drug application 50098. All patients or their legal representatives provided written informed consent, and children under the age of 18 years also provided assent. The study was conducted in accordance with the protocol, and all the authors vouch for the completeness and accuracy of the data and analyses. Study drugs were purchased by the sponsor. A patent for the topical formulation of WR 279,396 is owned by the U.S. Army. (For details about contributions of the authors, see the Supplementary Appendix, available at NEJM.org.)

STUDY TREATMENTS
The three types of cream (paromomycin–gentamicin, paromomycin alone, and vehicle control) were manufactured by Teva Pharmaceuticals in accordance with Good Manufacturing Practices. For each patient, all lesions (i.e., the index lesion plus nonindex lesions) were treated topically once daily for 20 days by a member of the study staff who documented the study treatment. (For details of the application procedures, see the Supplementary Appendix.)

STUDY PATIENTS
Inclusion criteria included an age of 5 to 65 years; overall good health besides cutaneous leishmaniasis; if female, absence of pregnancy and lactation; and the presence of five or fewer lesions, with an index lesion that was ulcerative, measured 1 to 5 cm in diameter, and was confirmed to contain leishmania by means of culture or microscopical examination of lesion material. Exclusion criteria included clinically significant lymphadenopathy or mucosal involvement, against which a topical agent would not be expected to be effective. (See the Supplementary Appendix and the protocol for all eligibility criteria.)

END POINTS

Efficacy
We assessed efficacy by measuring the area of the cutaneous leishmaniasis lesion at baseline and at 20 days (completion of treatment), 28 days, 42 days, 49 days, 98 days, and 168 days (end of the study). For each lesion, protocol-specified measures of response were as follows: initial clinical improvement (reduction in the area of the index lesion by 50 to 99% at 42 days, as compared with baseline), initial clinical cure (complete reepithelialization [no ulcer present] at 42 days, or initial clinical improvement followed by 100% reepithelialization by 98 days), relapse (initial clinical improvement or cure followed by an increase in lesion size or reulceration by 168 days), and final clinical cure (initial clinical cure without relapse). The protocol-specified primary efficacy end point was the final clinical cure of an index lesion.

The protocol-specified definition of treatment failure was an absence of initial clinical improvement or cure or an absence of final clinical cure. In addition, withdrawal of the patient before the end of the study because either the patient or the investigator thought the lesion was unlikely to have a response constituted treatment failure, as did loss to follow-up.

Safety
The safety end points were adverse events and application-site reactions (i.e., patients’ assessment of pain and irritation or clinicians’ assessment of erythema, edema, and vesicles). Safety end points were assessed daily during therapy. Renal toxic effects and ototoxic effects from aminoglycoside exposure were ascertained by means of serum creatinine measurements at the end of therapy (at 20 days) and patients’ daily reports of tinnitus and vertigo.

STATISTICAL ANALYSIS
The sample size of 375 patients was based on estimated rates of final clinical cure of 94% in the paromomycin–gentamicin group and 71% in
the vehicle-control group, as shown in a previous study. On the basis of these rates, a sample size of 125 patients in each of these two groups provided a statistical power of 99% to detect a significant difference in the rates of final clinical cure rates (94% vs. 71%). For powering the study, it was postulated that the cure rate in the paromomycin group would be between the rates in the paromomycin–gentamicin group and the vehicle-control group.

The modified intention-to-treat population consisted of patients who received at least one dose of study treatment. We tested two hypotheses using a fixed testing-sequence procedure with an overall two-sided alpha level of 0.05 or less. The first null hypothesis was that there was no difference in the final clinical cure rate between paromomycin–gentamicin and vehicle control and there was no significant difference in the rate of a final clinical cure between the paromomycin group and the vehicle-control group. The second null hypothesis was that there was no significant difference in the rate of a final clinical cure between the paromomycin–gentamicin group and the paromomycin group. A two-sided uncorrected chi-square analysis was used to test these hypotheses. Thus, the study was designed to determine whether paromomycin–gentamicin or paromomycin alone was superior to vehicle control and whether the combination product (paromomyci-
cin–gentamicin) was superior to paromomycin alone (analytic details are provided in the Supplementary Appendix).

**RESULTS**

**PATIENTS**

Of the 1432 screened patients, 383 were randomly assigned to receive a study treatment. A total of 375 received an investigational product and constituted the modified intention-to-treat population (Fig. 1). Patient characteristics are shown in Table 1 and in the Supplementary Appendix. Approximately half the patients were male and adult. Patients had 1 to 5 lesions, and 58% had more than one lesion. The lesion size was significantly larger in the paromomycin–gentamicin group than in the other two groups. A total of 797 lesions were treated. Essentially all lesions were ulcerative. The majority of lesions were on the lower limbs, followed by the upper limbs, head, and torso. We determined the parasite species of 78% of the index lesions; all were *L. major*.

**TREATMENT COMPLIANCE**

Of the 375 patients, 371 (99%) completed all 20 days of treatment. One patient receiving paromomycin alone and 3 receiving vehicle withdrew consent before completing all 20 days of study cream administration.

**EFFICACY**

The rate of final clinical cure of the index lesion, the primary efficacy end point, was 81% (95% confidence interval [CI], 73 to 87) with paromomycin–gentamicin, 82% (95% CI, 74 to 87) with paromomycin alone, and 58% (95% CI, 50 to 67) with vehicle control (P<0.001 for each active-drug group vs. the vehicle-control group) (Table 2). Paromomycin–gentamicin and paromomycin alone performed equally well in this study.

The primary reason for failure was an absence of initial improvement by 42 days, which occurred with the vehicle control approximately twice as often as in each active-drug group (Table 2). The next most common reason for failure was relapse, which generally consisted of enlargement by 49 days after initial improvement at 42 days. More patients had a relapse in each active-drug group than in the vehicle-control group (Table 2). There were eight withdrawals before a protocol-specified evaluation time point because the investigator or patient perceived an absence of response. Seven other patients withdrew for other reasons, did not complete therapy, or were lost to follow-up (Fig. 1 and Table 2).

Although the protocol-specified primary end point was cure of the index lesion, the absence of a response in any lesion constitutes treatment failure for the patient. Therefore, the rate of cure of all lesions is of clinical interest. One patient in each of the active-drug groups and three patients in the vehicle group had a nonindex lesion that was not cured (Table 2). Therefore, 80% of patients receiving paromomycin–gentamicin and 81% of those receiving paromomycin alone had all lesions cured, as compared with 56% of patients receiving vehicle control (P<0.001 for both comparisons).

Although the protocol-specified criteria for cure (improvement at an early time point of 42 days, cure at an intermediate time point of 98 days, and no relapse by 168 days) are in accord with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paromomycin–Gentamicin (N = 125)</th>
<th>Paromomycin Alone (N = 125)</th>
<th>Vehicle Control (N = 125)</th>
<th>All Patients (N = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>56 (45)</td>
<td>68 (54)</td>
<td>69 (55)</td>
<td>193 (51)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>23±16</td>
<td>25±16</td>
<td>23±15</td>
<td>24±16</td>
</tr>
<tr>
<td>Age &gt;17 yr — no. (%)</td>
<td>63 (50)</td>
<td>66 (53)</td>
<td>61 (49)</td>
<td>190 (51)</td>
</tr>
<tr>
<td>Total no. of lesions in group</td>
<td>243</td>
<td>272</td>
<td>282</td>
<td>797</td>
</tr>
<tr>
<td>Area of all lesion ulcers per patient — mm²</td>
<td>126±121</td>
<td>90±75</td>
<td>98±112</td>
<td>105±105</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant differences among groups.
clinical practice, some clinicians may expect a treatment to provide a cure at an early time point. The percentage of all lesions that were 100% healed at 42 days were 79%, 83%, and 57% in the paromomycin–gentamicin, paromomycin, and vehicle-control groups, respectively (P<0.001 for each active-drug treatment group vs. the vehicle-control group) (Table 2). The typical response of a lesion to treatment is shown in Figure 2.

The mean area of ulceration of the index lesion increased between 1 day and 20 days (the end of therapy) in the paromomycin–gentamicin group and in the paromomycin group but not in the vehicle-control group, with no withdrawals or treatment interruptions because of this reaction. By 28 days, however, the size of the mean lesion in the active-drug groups had decreased to approximately baseline levels.

### Table 2. Efficacy Outcomes in the Modified Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Paromomycin–Gentamicin (N = 125)</th>
<th>Paromomycin Alone (N = 125)</th>
<th>Vehicle Control (N = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final clinical cure of index lesion (primary end point) — no. (%)‡</td>
<td>101 (81)</td>
<td>102 (82)</td>
<td>73 (58)</td>
</tr>
<tr>
<td>Final clinical cure of index lesion but not all nonindex lesions — no.†</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lack of final clinical cure of index lesion — no.</td>
<td>24</td>
<td>23</td>
<td>52</td>
</tr>
<tr>
<td>Index lesion not cured — no.</td>
<td>23</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>No improvement at 42 days — no.</td>
<td>19</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>Relapse — no.</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Improvement at 42 days but enlargement at 49 days — no.</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Reepithelialization at 42 days but enlargement at 49 days — no.</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal by investigator or patient owing to disease progression — no.§</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Withdrawal by patient for other reason — no.</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Incomplete treatment or lost to follow-up — no.</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total reepithelialization of ulcerated lesions at 42 days — no./total no. of ulcerated lesions at baseline (%)§</td>
<td>190/240 (79)</td>
<td>218/262 (83)</td>
<td>160/279 (57)</td>
</tr>
</tbody>
</table>

‡ The absolute difference in the rates of the primary end point was 23 percentage points (95% confidence interval [CI], 11 to 34; P<0.001) between paromomycin–gentamicin and vehicle control, 24 percentage points (95% CI, 12 to 34; P<0.001) between paromomycin alone and vehicle control, and –1 percentage point (95% CI, –10 to 9; P = 0.87 by a two-sided uncorrected chi-square test) between paromomycin–gentamicin and paromomycin alone.

† In cases in which a final clinical cure occurred in the index lesion but not all nonindex lesions, all nonulcerated lesions were cured, including the one nodular lesion.

§ Of the eight patients who were withdrawn owing to disease progression, the patient in the paromomycin group was withdrawn by the investigator because of lymphangitis (suspected disease dissemination). The remaining seven patients were in the vehicle-control group: three were withdrawn by the investigator because the index lesion had increased in size by 28 days; one had index-lesion enlargement by a factor of 1.6 by 20 days, accompanied by development of three new lesions; two had index-lesion involution by 49 days; and one withdrew consent at 28 days because the index lesion had not changed in size. The effect of the lack of definitive end-point determination with respect to patients lost to follow-up was explored (see the Supplementary Appendix).

§ Complete reepithelialization occurred in significantly more lesions in either active group than in the vehicle-control group (P<0.001 for each comparison, by a two-sided uncorrected chi-square test).

### SAFETY

All adverse events that were deemed by the investigators as at least possibly related to a study treatment were reactions of mild or moderate severity at the application site. Adverse events that occurred in at least 1% of patients in any group are shown in Table 3. Erythema and skin irritation were present in all groups; the latter was attributed to the dressing. Minute vesicles were significantly more frequent in the active-drug groups than in the vehicle-control group. Superinfection (clinical signs of secondary bacterial infection of cutaneous leishmaniasis lesions) was significantly more common in the vehicle-control group than the active groups. One serious adverse event — acute poststreptococcal glomerulonephritis — occurred in the paromomycin–gentamicin group and was considered to be unrelated to the study treatment.

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<table>
<thead>
<tr>
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<td>1</td>
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§ Complete reepithelialization occurred in significantly more lesions in either active group than in the vehicle-control group (P<0.001 for each comparison, by a two-sided uncorrected chi-square test).
There were no cases of clinically significant tinnitus or vertigo or changes in serum creatinine levels between screening and the evaluation at 20 days, and no patient was removed from the study owing to an adverse event. There were no deaths.

**DISCUSSION**

This trial showed that either of two creams containing 15% paromomycin, one with and one without 0.5% gentamicin, was superior in efficacy to a vehicle-control cream for treating ulcerative cutaneous leishmaniasis caused by *L. major* in Tunisia. There was no advantage in the addition of gentamicin observed in this study. The index lesion was cured in 101 of 125 patients (81%) receiving paromomycin–gentamicin, in 102 of 125 patients (82%) receiving paromomycin alone, and in 73 of 125 patients (58%) receiving vehicle control (*P*<0.001 for each paromomycin group vs. the vehicle-control group).

Our phase 3 study was conducted on the basis of successful results of a previous phase 2 study conducted in both Tunisia and Paris. A comparison of the results of these two studies is provided in the Supplementary Appendix.

Paromomycin–gentamicin and paromomycin alone, when administered to leishmaniasis-induced ulcers for 20 days, resulted in systemic paromomycin exposure that was less than 10% of the exposure from a standard regimen of intramuscular paromomycin. Thus, as expected, there were no instances of clinically meaningful renal toxic effects or ototoxic effects in this trial. The formation of minute vesicles was more frequent in the active-drug groups than in the vehicle-control group. Clinicians and patients should anticipate that when either active cream is used, a transient inflammatory reaction involving lesion enlargement and vesicle formation may occur during treatment. However, no patient requested to withdraw or had treatment suspended because of this inflammatory reaction; there were

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**Figure 2. Response of a Typical Lesion to Treatment with Paromomycin–Gentamicin.**

On the first day of the study, the ulceronodular facial lesion was 24.0 mm by 19.7 mm in area (Panel A). By 20 days, at the end of therapy, the lesion had visibly flattened (Panel B) and measured 2.1 mm by 1.1 mm in area. There was complete reepithelialization of the lesion by 42 days (Panel C), and the lesion had not relapsed by 157 days (Panel D).
no problems with compliance. We postulate that the inflammatory reaction aids ulcer resolution. Superinfection was more common with vehicle control than with paromomycin, which we attributed to an absence of local antibacterial effect of the aminoglycosides. All superinfections were treated with oral antibiotics and resolved.

This trial provides evidence that either paromomycin formulation in the present hydrophilic vehicle control is an effective treatment for ulcerative *L. major* disease in Tunisia. Early treatment of *L. major* cutaneous leishmaniasis with a cream is simpler than the current treatment options for cutaneous leishmaniasis and follows the recent WHO recommendations for the treatment of *L. major* cutaneous leishmaniasis.\(^1\)

The similarity in the natural cure rate for *L. major* infection in such geographically separate areas as Tunisia\(^2\) and Iran\(^3\) suggests that either cream would be effective treatment for ulcerative *L. major* in general, although studies are needed to address this expectation. The efficacy of these creams against nonulcerative disease or disease caused by other species of leishmania remains to be fully investigated. In this regard, we note that in animals, paromomycin–gentamicin and paromomycin alone were equally effective against *L. major*, a result that predicted the findings of our study, but paromomycin–gentamicin was more effective than paromomycin alone against American species such as *L. panamensis* and *L. amazonensis*.\(^26\) For all cases of cutaneous leishmaniasis, the therapeutic index for the two paromomycin creams is enhanced by their acceptable side-effect profile, as compared with alternative interventions.

The opinions or assertions expressed in this article are the views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

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Table 3. Adverse Events Occurring in More Than 1% of Patients in Any Study Group.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Paromomycin–Gentamicin (N = 125)</th>
<th>Paromomycin Alone (N = 125)</th>
<th>Vehicle Control (N = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Application site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>6 (5)</td>
<td>0</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inflammation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vesicles</td>
<td>26 (21)</td>
<td>5 (4)</td>
<td>27 (22)</td>
</tr>
<tr>
<td>Edema</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pain</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5 (4)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Superinfection</td>
<td>3 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>4 (3)</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>9 (7)</td>
</tr>
</tbody>
</table>
REFERENCES


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