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EFFICACY AND SAFETY OF ELICA-M™ CREAM (MOMETASONE FUROATE 0.1% W/W AND MICONAZOLE NITRATE 2% W/W) IN NAPKIN DERMATITIS OR DERMATITIS CAUSED BY INFECTION WITH CERTAIN FUNGI AND BACTERIA IN CHILDREN ZERO TO THREE YEARS OF AGE AN OPEN-LABEL, PHASE IV, MULTICENTER STUDY

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ABSTRACT

Background: Napkin dermatitis is a skin condition that affects the area under a baby's diaper. It is a very common dermatological disease in infants and children, mainly caused by excess moisture of the skin, or prolonged contact with urine and feces. **Objective:** Our study aimed to assess the efficacy and safety of Elica-M™ cream in children with napkin dermatitis with inflamed skin conditions of eczema or dermatitis caused by fungal and bacterial infections. **Methods:** This was an open-label, single-arm, phase IV study to evaluate the safety and efficacy of Elica-M™ cream in 69 children with napkin dermatitis with inflamed skin conditions of eczema or dermatitis caused by infection with certain fungi and bacteria. We conducted our study at two centers in the Kingdom of Saudi Arabia. All enrolled subjects were treated for 14 days and followed up for efficacy and safety assessments. **Results:** Efficacy evaluation showed that around 90% of patients had more than 50% reduction in the signs of erythema and pruritus. Meanwhile, evaluation of severity showed that at the baseline visit, the grades were 29%, 66.7% and 4.3% for mild, moderate, and severe, respectively. Finally, only two patients experienced moderate adverse events; not serious and were found to be unrelated to the study medication. **Conclusion:** The evaluation of the efficacy of Elica-M™ cream showed a substantial reduction in the signs and symptoms of erythema and pruritus. Additionally, the two moderate, adverse events reported indicate the high safety feature of Elica-M™ cream.

KEYWORDS: Elica-M™ Cream, Napkin Dermatitis, Dermatitis, Eczema, Mometasone Furoate, Miconazole Nitrate.

INTRODUCTION

Napkin dermatitis, also known as diaper rash, is a skin condition that affects the skin under a baby's napkin, mainly due to overhydration of the skin, excess moisture, or prolonged contact with urine and feces. It describes any of a group of inflammatory skin conditions that occur in the diaper area. It is considered one of the most commonly encountered dermatologic diseases affecting infants and children. Napkin dermatitis usually presents as erythematous papules and macules in the genital area of the infant and can sometimes spread to the lower abdomen and thighs.[1, 2] Some bacteria such as group A streptococci or *Staphylococcus aureus (S. aureus)* can cause eruptions in that area. *S. aureus* colonization is frequently found in children with Atopic dermatitis (AD) and children with diaper rash. [3] When diaper dermatitis is complicated by *Candida albicans (C. albicans)* infections, a topical antifungal is required.[4, 5] Miconazole nitrate has shown effective results against *C. albicans*.[6–8] Traditional treatments for diaper dermatitis encompass the application of topical steroids, antifungals, and a combination of both.[4, 9]

Topical corticosteroids were considered the main pillar of medicated therapy for AD and other types of dermatitis, including napkin dermatitis, since their introduction in 1952[1, 2, 10], when topical hydrocortisone effectively treated selected dermatoses.[11] Topical corticosteroids reflect the mainstay of therapy that adequately controls acute flares of AD in both children and adults.[12]

The chief milestone achieved in dermatologic therapy is the availability of glucocorticosteroids, owing to their potent anti-inflammatory effects.[13] However, the mechanisms of action that are responsible for their therapeutic effect and the improvement of dermatologic inflammatory conditions may cause adverse effects. The first reported adverse effects related to topical

corticosteroids appeared in 1955 after the use of fludrocortisone.[14]

Mometasone furoate is a topical corticosteroid that was proven to be mid-potent in dermatological use. It has anti-inflammatory, vasoconstrictive, and anti-pruritic properties. Corticosteroids induce lipocortins; phospholipase A2 inhibitory proteins. These proteins control and influence the biosynthesis of inflammatory mediators, such as leukotrienes and prostaglandins, by impeding the release of the common precursor arachidonic acid. Mometasone furoate is used to treat scalp psoriasis, psoriasis vulgaris, AD, and napkin dermatitis.[15]

Miconazole nitrate is an antifungal agent, an imidazole derivative with a broad activity spectrum. It inhibits cytochrome P450 complex (included in the biosynthesis process of fungi cell membranes), exhibiting a fungistatic effect. Additionally, it exhibits a fungicidal effect against certain fungal species due to the accumulation of hydrogen peroxide resulting from disturbances in peroxidative and oxidative enzyme activities. Miconazole nitrate also has substantial activity against *C. albicans*, dermatophytes, and Gram-positive bacteria.[16, 17]

The only topical steroid that has been approved for use in children in the US is Mometasone furoate. Even 0.5% and 1% concentrations of hydrocortisone formulations, which are available as over the counter medications, are not approved for use in children.[12]

Though topical corticosteroids are clinically effective, they are easily absorbed through the skin, which is cause for concern, especially when treating infants suffering from dermatitis, because their skin is more permeable than adult skin and has the ability to absorb greater quantities of the medication. Tests have shown that topically applied corticosteroids have the potential to cause suppression of the hypothalamic-pituitary axis (HPA) with possible impairment of growth. [18, 19] Additionally, systemic absorption of topical corticosteroids can cause systemic implications, including iatrogenic Cushing disease and adrenal suppression.[20–22]

Infants and young children are at a higher risk for significant adrenal suppression, also, those in whom corticosteroids are applied over large areas, and those with impaired cutaneous barriers. Highly vascular areas, like the diaper area, have been linked to enhanced systemic absorption.[23]

Our study aimed to evaluate the safety and efficacy of the combination of Mometasone furoate (0.1% W/W) and Miconazole nitrate (2% W/W) in children with napkin dermatitis with inflamed skin conditions of eczema or dermatitis caused by fungal and bacterial infections.

MATERIALS AND METHODS

1. Study Design

We conducted an open-label, non-randomized, single-group, phase IV study to evaluate the efficacy and safety of Elica-M™ cream. The date of the first visit was 11-May-16, and the last visit was 02-Jan-17.

2. Population

In our study, 69 children aged 0 to 3 years with napkin dermatitis with inflamed skin conditions of eczema or dermatitis caused by a fungal or bacterial infection were enrolled from two centers in the Kingdom of Saudi Arabia. All subjects met the inclusion criteria and signed informed consent forms.

Subjects who were included in the study were male and female subjects 0 to 3 years of age, diagnosed with eczema or dermatitis caused by an infection with certain fungi and bacteria. Parents of the study participating children must have agreed not to treat dermatitis or eczema with other topical or systemic therapies during the study, and were able to understand the procedures of the protocol and follow the requirements during the course of the study, and signed the informed consent form and ensured availability for all study visits.

On the other hand, subjects who were excluded from the study were those who had any chronic condition that was not well controlled and other serious skin disorders, pigmentation, or extensive scarring in affected areas; those who had hypersensitivity to antifungal drugs or any of the ingredients of the study drug, and those who used any investigational medication or systemic medication within four weeks prior to the start of the study drug or five pharmacokinetic/pharmacodynamic half-lives (whichever was longer). Any subjects with a history of congenital or acquired immunodeficiency; any concurrent illness that will affect the safety of subjects in the trial, significant cardiovascular, hepatic and renal diseases which, in the opinion of the investigator, will preclude the subject from participation, and those who participated in any other clinical trial 30 days prior to screening were also excluded.

Ethical Conduct of the Study

This study complied with the recommendations of the 18th World Health Congress (Helsinki, 1964) and all the applicable amendments, as well as the laws and regulations and any applicable guidelines of the Kingdom of Saudi Arabia where the study was conducted.

3. Study Medication

Subjects were required to apply Elica-M™ cream (Mometasone furoate 0.1% w/w and Miconazole nitrate 2% w/w) twice daily for two weeks. The success of the treatment was defined as ≥ than 50% reduction in the signs and symptoms of the disease based on the Physician Global Evaluation of Clinical Response.

Safety was assessed throughout the study by observing the incidence of adverse events.

Elica-M™ cream contains a combination of mometasone furoate 0.1% w/w and miconazole nitrate 2% w/w. Miconazole nitrate is an antifungal agent known to destroy fungal infections and some of the associated bacteria while mometasone furoate is a topical steroid which reduces inflammation, swelling, redness, and itching of the skin.

No other medications for napkin dermatitis with inflamed conditions of eczema and dermatitis were allowed during the study, and medications for any other illness was allowed as per the investigator's discretion. Rescue medications were only allowed in severe cases as per the investigator's discretion.

4. Outcome Measures

Dermatitis or eczema was examined by the principal investigator on the entire body of the subject, which was divided into five major areas; head and neck, trunk, back, upper limbs, and lower limbs for the trial's purpose. The principal investigator selected a target area for the assessment of the primary efficacy. The target area was defined as an area where maximum signs and symptoms of dermatitis or eczema are present. The number and the percentage of patients in each category of the target area were reported.

4.1. Efficacy Variables

The efficacy variables included improvement by ≥ 50% of the individually measured signs of the disease (erythema, pruritus, and scaling) in the target area from baseline (Day 0) to the end of the study (Day 14), using the Physician Global Evaluation of Clinical Response. The percentage of patients showing improvement was calculated, and a significant improvement was evaluated using the Chi-square test.

The intensity of the lesions was determined after evaluating the signs and symptoms of dermatitis and eczema in the target area in order to define the improvement in grades of erythema, scaling and pruritus from baseline to study day 14, using the Physician Global Evaluation of Severity. The average score of the patients at baseline and day 14 were reported. A significant change in the score at day 14 versus baseline was tested using dependent student t-test.

4.2. Safety Variables

Regarding the safety assessments, adverse events were collected using either a spontaneous report by the subject's parent or discovered by the investigator's questioning, physical examination or clinical laboratory evaluations during the assessment visits. Investigators documented and reported all adverse events (AEs) according to procedures outlined in the study protocol. The nature, time of onset, duration and severity of all AEs were documented, together with the Investigator's opinion of the relationship to drug administration. The study staff instructed the subject to record all AEs in the subject diary.

4.3. Statistical Analysis

The sample size was based on the assumption of a 20% improvement in the success rate from baseline to day 14 of treatment in erythema and pruritus. Around 55 subjects would be required to detect the expected percent change, assuming that 5% of the wounds would heal with no treatment. A total of around 66 subjects would be required to be enrolled in the study considering a 20% dropout rate. The analysis population was the Intent-to-Treat Population (ITT) who entered the study and successfully followed up to visit 3 (Day 7±2).

RESULTS

1. Demographics and Baseline Characteristics

The total number of patients recruited in the study was 69, selected from two sites. The date of the first visit was 11-05-2016, and the last visit was 02-01-2017. All patients met the inclusion criteria, and their parents signed informed consent forms on their behalf.

Patients who participated in the study showed different demographical and clinical characteristics. The gender was roughly equally distributed between males (52.2%) and females (47.8%), with a mean age of 27.58 months (± 8.08). The dominant race was Caucasian (91.3%), followed by Middle Eastern (7.2%), and Hispanic (1.4%). The average weight of the patients was 13.54 kg (± 2.85), with a height of 92.06 cm (± 15.37). There was no statement of surgical history except for one patient. (Table 1)

Table 1: Demographics and baseline characteristics.

Patients' characteristics	Baseline values
Gender	
Male, n (%)	**36 (52.2%)**
Female, n (%)	**33 (47.8%)**
Age (Mean, SD, in months)	**27.58 (8.08)**
Age (Median, IQR, in months)	**28 (7)**
Systolic blood pressure (Mean, SD in **mmHg)**	**101.06 (9.95)**
Diastolic blood pressure (Mean, SD **in mmHg)**	**59.56 (7.32)**
Sitting Pulse Rate (Mean, SD **in beats/min)**	**101.18 (30.87)**
Respiratory Rate (Mean, SD **in breaths/min)**	**27.20 (5.88)**
Oral Temperature ^{o}C (Mean, SD)	**36.75 (0.38)**
Weight (Mean, SD, in kg)	**13.54 (2.85)**
Height (Mean, SD, in cm)	**92.06 (15.37)**
Race	
Caucasian, n (%)	**63 (91.3)**
Middle Eastern, n (%)	**5 (7.2)**
Hispanic, n (%)	**1 (1.4)**
Medical-surgical history	
Yes, n (%)	**1 (1.4)**
No, n (%)	**68 (98.6)**
Disease Assessment	
Mild	**20 (29)**
Moderate	**46 (66.7)**
Severe	**3 (4.3)**

The disease assessment showed that 71% of the patients had severe and moderate symptoms, and 29% had mild symptoms. The distribution of the disease was mainly located in the lower limbs (26.1%), followed by the trunk (23.2 %), the head and neck (20.3%), the back (17.4%), and the upper limbs (13%). (Fig. 1)

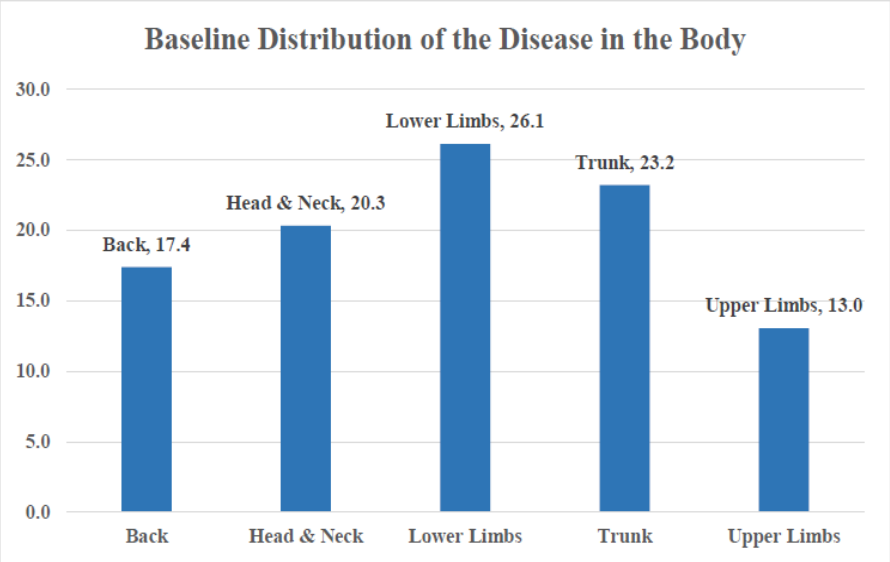

Figure 1: Baseline distribution of the disease.

Four patients reported the concomitant intake of medications during the study period. The medications taken were multivitamins to enhance immunity, paracetamol to treat fever, fusidic acid topical cream to treat a lesion on the right cheek, and potassium permanganate to heal wounds.

2. Study Outcomes

2.1. Efficacy Outcomes

2.1.1. The Physician Global Evaluation of Clinical Response

Patients undergoing treatment showed a substantial reduction in the measured signs of erythema and pruritus as reported by the Physician Global Evaluation of Clinical Response, where 90% of subjects showed more

than 50% reduction in the symptoms on day 7, achieving the first primary objective of the study of at least 50% improvement by visit 3. Moreover, at the end of the study (Day 14), only 1.4% of subjects experienced less than 50% reduction in the symptoms, and more than 80% of subjects experienced 100% reduction in the symptoms, with a 95% confidence interval of 70.8-89.0 for the population percentage. (Fig. 2)

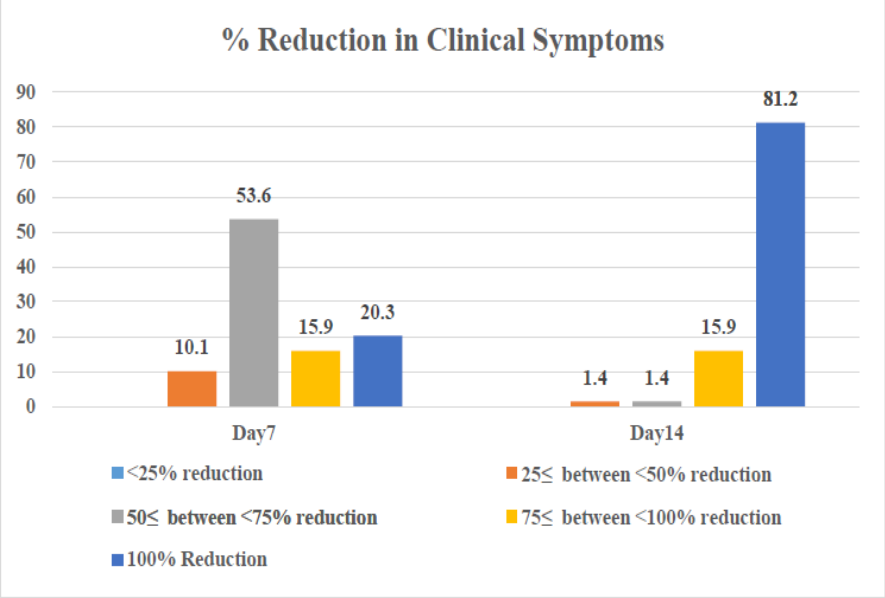

Figure 2: Percent reduction in clinical symptoms on day 7 and day 14.

2.1.2. The Physician Global Evaluation of Severity

The severity of the disease was assessed by the Physician Global Evaluation of Severity. At baseline, the grades were 29%, 66.7% and 4.3% for mild, moderate and severe, respectively. After seven days, the disease signs were absent in 14 subjects (20.3%), mild in 51 subjects (73.9%), and moderate in four subjects (5.8%). By day 14, only six subjects (8.7%) had mild symptoms, and the remaining 63 subjects (91.3%) had no symptoms. (Fig. 3)

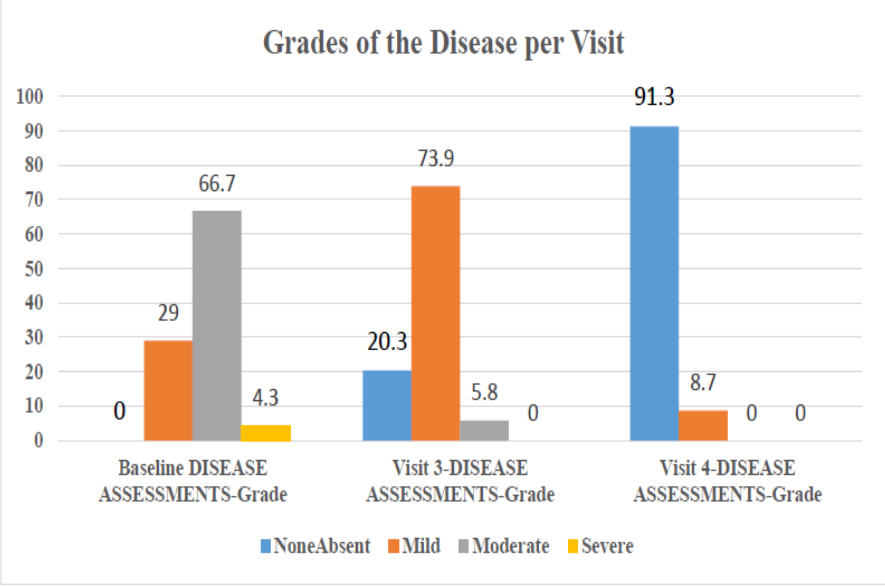

Figure 3: Grades of the disease per visit.

2.2. Safety Outcomes

Only two out of the 69 subjects experienced adverse events; diarrhea and fever. The two adverse events were moderate and not serious in severity and were found to be unrelated to the study medication. Additionally, the two adverse events did not last for long (the longest duration was two days). Medication was given to one of the patients who experienced an adverse event, and there was an improvement and complete recovery for the two cases. (Table 2)

Table 2: Adverse events.

Adverse events		Frequency	Percent
No		67	97.1
Yes	Diarrhea	1	1.4
	Fever	1	1.4
Total		69	100.0

DISCUSSION

In our study, our objective was to evaluate the safety and efficacy of Elica-M^{TM} cream, a combination of Mometasone furoate (0.1% W/W) and Miconazole nitrate (2% W/W), in children 0-3 years of age with napkin dermatitis with inflamed skin conditions of eczema or dermatitis caused by fungal and bacterial infections.

Several studies exploring the effectiveness of miconazole nitrate cream showed very promising results. In an old study dating back to 1974, 2% miconazole nitrate cream successfully treated candida skin infections in the diaper area of children and infants, both maturely and prematurely born.[24, 25] Over three decades later, two trials compared 0.25% miconazole nitrate ointment with an ointment base for the treatment of acute infant diaper dermatitis complicated by candidiasis. The 0.25% miconazole nitrate ointment was significantly more efficient and safer than the ointment base in treating diaper dermatitis.[4, 8, 26] In a 1993 study where moderate to severe diaper dermatitis was being treated, systemic absorption of 0.25% miconazole nitrate ointment was minimal, which demonstrates its safety, seeing as 83% of participating infants (15 out of 18) had undetectable (<1 ng/mL) blood concentrations of miconazole during the 7-day period of the study, which included a total of 28 dosing times.[6, 7] All three findings concur with this study's results, as miconazole nitrate was found to be effective and safe for the treatment of diaper rash. Even though two of the 69 patients participating in this study experienced diarrhea and fever, those adverse events were unrelated to the medication. About 90% of subjects showed more than 50% reduction in the symptoms on day 7, achieving the first primary objective of the study of at least 50% improvement. Moreover, at the end of the study, only 1.4% of subjects experienced less than 50% reduction in the symptoms, and 80% of subjects experienced 100% reduction in the measured signs of erythema and pruritus reported by the Physician Global Evaluation of Clinical Response.

Topical steroids have become the main treatment of atopic dermatitis, but they may cause side effects from systemic absorption, particularly in children. Mometasone furoate, a moderate-potency steroid, appeared to have a significant anti-inflammatory potency with less inhibitory effects on the hypothalamic-pituitary-adrenal axis (HPA).[27, 28] However, the percutaneous absorption of mometasone furoate was found to be low (around 0.4% for the cream and 0.7% for the ointment, making the cream safer) and when it enters the circulation, it undergoes biotransformation in the liver into three different metabolites with very little intrinsic activity.[29]

The British National Formulary emphasizes that children are particularly susceptible to side effects of topical corticosteroids, and that is why they recommend that in general, topical corticosteroids be avoided in children or, if necessary, used with great care and for short periods.[30] The most frequent adverse effects of corticosteroids include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura. And with lower frequency hypertrichosis, pigmentation alterations delayed wound healing and exacerbation of skin infections. More importantly is the rate of contact sensitization against corticosteroids, which is considerably higher than generally believed. Systemic reactions such as hyperglycemia, glaucoma, and adrenal insufficiency have also been reported.[31] Measures to prevent the side effects include the use of lower-potency steroids, the application only in the morning, and alternate-day treatment (reducing tachyphylaxis and avoidance of occlusion).[32] Additionally, in a study of 18 children, it was noted that weaker concentrations of topical corticosteroids under occlusion had comparable high efficacy but were associated with a lower risk of HPA suppression.[33]

A 6-week randomized, blinded study by Vernon compared the efficacy and safety of mometasone furoate 0.1% cream applied once daily, and hydrocortisone, 1.0% cream, applied twice daily, in 48 children with moderate to severe atopic dermatitis. Mometasone furoate produced significantly greater improvement than the low-potency hydrocortisone used twice daily. The difference in therapeutic response was particularly evident in patients with involvement of more than 25% of their body surface area, proving the high efficacy of mometasone furoate, which is also supported by the findings of this study. Mometasone also seems to be safe in young children and has fewer effects on the HPA axis than other mid-strength corticosteroids, however, it should still be prescribed with caution as any topical corticosteroid for prolonged use in children.[34]

Furthermore, in a comparative clinical safety and efficacy study of mometasone furoate 0.1% with dexamethasone, the Physician Global Evaluation of the overall change in disease status and the patients' evaluation of treatment also indicated that the two treatment regimens produced comparable, rapid and progressive improvements in the patients' conditions, and no local side effects were reported.[35]

Most topical steroids like mometasone, fluticasone, and methylprednisolone are recommended for once a day application.[36, 37] However, Elica-M™ Cream has been proven to be safe with the administration twice daily.

CONCLUSION

Results showed that there was a substantial reduction in the measured signs of erythema and pruritus. At the end of the study, the Physician Global Evaluation of Clinical Response showed that more than 80% of subjects had a 100% reduction in their symptoms. Furthermore, the assessment of disease severity, which was assessed by the Physician Global Evaluation of Severity showed that by the end of the study, only six subjects (8.7%) had mild symptoms, and all others were none or absent, achieving the secondary objective of 50% shift in one grade at day 7 and persisting until the end of the study. Regarding safety, only two adverse events were reported. They were of less significance, not serious in severity, and unrelated to the study medication, indicating the high safety feature of Elica-M™ Cream.

What's Known/What's New?

- Napkin dermatitis is typically treated with topical corticosteroids, antifungals, or a combination of both. However, the mechanisms by which these treatments perform their therapeutic effect may cause adverse effects.
- Elica-M™ cream showed substantial efficacy in the treatment of napkin dermatitis and reducing symptoms of erythema and pruritus.
- Only two moderate adverse events were reported, and they were unrelated to the drug, indicating the high safety feature of Elica-M™ cream.

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CONFLICT OF INTEREST

The authors have no conflicts of interests to declare.

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