

Table of Contents

In memoriam

- Aleksej Kinsky, 1925–2015** 65
Jovan Miljković

Letter to the Editor

- Abdominopelvic post-irradiation morphea in a prostate cancer patient: the first case of an under-recognized condition** 67
Nicola di Meo, Cecilia Noal, Sara Trevisini, Bruno Ulessi, Giusto Trevisan

Original articles

- Ecthyma gangrenosum versus ecthyma-like lesions: should we separate these conditions?** 69
Michael Vaiman, Tsilia Lasarovitch, Lior Heller, Gad Lotan

- Plasma-soluble urokinase plasminogen activator receptor (suPAR) levels in psoriasis patients and correlation with disease severity** 73
Gülcan Saylam Kurtipek, Recep Kesli, Fatma Tunçez Akyürek, Fikret Akyüret, Yüksel Terzi

Case reports

- Parry–Romberg syndrome: a case with a possible association with Lyme disease** 77
Nicola di Meo, Giuseppe Stinco, Katuscia Nan, Caterina Pinzani, Giusto Trevisan

- Successful removal of hyperkeratotic-lichenoid reaction to red ink tattoo with preservation of the whole tattoo using a skin grafting knife** 81
Boštjan Mlakar

Belakne (adapalen)

Adapalen je **ZDRAVILO IZBORA ZA ZDRAVLJENJE BLAGIH DO ZMERNIH OBLIK AKEN.**

(European Evidence based Guidelines for the Treatment of Acne, JEADV 2012)



Zdravilo Belakne **DELUJE NA VZROK** nastajanja aken

PROTIVNETNO

**URAVNAVA
DIFERENCIACIJO
KERATINOCITOV**

KOMEDOLITIČNO

PROTIBAKTERIJSKO

ZA OPTIMALEN REZULTAT ➡ Belakne – v dveh oblikah



gel 0,1%
za mastno kožo

krema 0,1%
za suho, občutljivo kožo

Skrajsan povzetek glavnih značilnosti zdravila

Belakne 1 mg/g gel

Belakne 1 mg/g krema

Sestava: 1 g gela ali kreme vsebuje 1 mg adapalena.

Indikacije: Zdravljenje blagih do zmernih aken s pretežno prisotnimi ogrci, papulami in pustulami na obrazu, prsih ali hrbtu.

Odmerjanje: Zdravilo Belakne se uporablja pri otrocih starejših od 12 let in pri odraslih. Varnost in učinkovitost zdravila Belakne pri otrocih, mlajših od 12 let nista bili dokazani. Zdravilo Belakne je treba nanesti na aknozne spremembe kože enkrat na dan, najbolje po umivanju, zvečer pred spanjem. Tanko plast kreme ali gela je treba z blazinicami prstov nanesti na prizadeta mesta na koži tako, da se izogiba očem in ustnicam. Priporočljivo je, da se oceni izrazitost izboljšanja po 3 mesecih zdravljenja z zdravilom Belakne. Če je potrebno zdravljenje s percutanimi protibakterijskimi zdravili ali benzoil peroksidom, jih je treba na kožo nanašati zjutraj, zdravilo Belakne pa zvečer.

Kontraindikacije: Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov.

Posebna opozorila in previdnostni ukrepi: Če se pojavi preobčutljiva reakcija ali hudo draženje, je treba uporabo zdravila prekiniti. Zdravilo Belakne ne sme priti v stik z očmi, usti, robovi nosu ali mukoznimi membranami. Če zdravilo po nesreči pride v stik z očmi, jih je treba izprati s toplo vodo. Ne sme se aplicirati na poškodovano (ureznine in odrgnine), od sonca opečeno ali ekcematozno kožo niti se ga ne sme uporabljati pri bolnikih s hudimi aknami ali aknami na večjih površinah telesa. Pri bolnikih, ki prejemajo retinoidna zdravila se je treba izogibati depilaciji z voskom. Hkrati uporabi zdravila Belakne in percutanih keratolitikov ali eksfoliacijskih zdravil se je treba izogibati. Ob sočasni uporabi sredstev za luščenje (peeling), medicinskih ali abrazivnih mil, kozmetičnih izdelkov, ki kožo sušijo, adstringentov ali izdelkov, ki dražijo kožo (dišav, lupino limone ali izdelkov, ki vsebujejo alkohol), se lahko stopnjuje učinek draženja. Izpostavljanje sončni svetlobi ali umetnim UV žarkom (vključno s solariji) je treba med uporabo zdravila Belakne zmanjšati na minimum. Kadar se izpostavljenosti soncu ni moč izogniti, je treba uporabljati zaščitna sredstva in zdravljene predele kože zaščititi z obleko.

Interakcije: Ni znanih interakcij pri sočasni uporabi zdravila Belakne z drugimi zdravili, ki jih lahko uporabljamo percutano. Kljub temu pa zdravila Belakne ne smemo uporabljati skupaj z drugimi retinoidi ali zdravili s podobnim načinom delovanja. Izogibati se je treba uporabi zdravila Belakne skupaj z vitaminom A (vključno s prehranskimi dodatki). Adapalen ni fototoksičen in ne povzroča alergije na svetlobo, vendar pa varnost uporabe adapalena med večkratno izpostavljenosti soncu ali UV sevanju ni bila dokazana. Večji izpostavljenosti soncu ali UV sevanju se je treba izogibati. Ker je absorpcija adapalena skozi kožo majhna, so interakcije s sistemsko uporabljenimi zdravili zelo malo verjetne.

Nosečnost in dojenje: Ker je na voljo malo podatkov in zaradi možnega prehoda zdravila skozi kožo v krvni obtok, zdravljenje z zdravilom Belakne med nosečnostjo ni priporočljivo. V primeru nepričakovane nosečnosti je treba zdravljenje z zdravilom Belakne prekiniti. Zdravilo Belakne lahko uporabljate med dojenjem, vendar se zdravila ne sme nanašati na predel prsnega koša, da ne pride v stik z dojenčkom. Učinkov adapalena na dojenčka ni pričakovati, ker je sistemska izpostavljenost doječe matere zanemarljiva.

Vpliv na sposobnost vožnje in upravljanja s stroji: Ni vpliva.

Neželeni učinki: Suha koža, draženje kože, občutek toplote na koži, eritem, kontaktni dermatitis, občutek nelagodja na koži, pekoč občutek na koži, srbenje, luščenje kože, očitno poslabšanje aken, bolečina, oteklina, mehurji ali kraste na koži in draženje, rdečina, srbenje ali oteklina očesnih vek.

Vrsta ovojnine in vsebina: Škatla s tubo po 30 g gela ali 30 g kreme.

Režim izdaje: Rp

Imetnik dovoljenja za promet: Belupo d.o.o., Dvorčakova 6, 1000 Ljubljana.

Datum zadnje revizije besedila: 28.5.2012

Podrobnejše informacije o zdravilu in povzetek glavnih značilnosti zdravila so vam na voljo pri strokovnih sodelavcih in na sedežu podjetja Belupo.

In Memoriam: Aleksej Kansky, 1925–2015



Our teacher, mentor, and colleague of many years, Aleksej Kansky, passed away on October 6th, 2015.

Aleksej Kansky was born in Ljubljana on February 23rd, 1925, where he attended classical secondary school and then graduated from the Faculty of Medicine in 1951. After completing his internship, he studied chemistry for eight semesters at the Faculty of Natural Sciences and Mathematics.

From 1955 to 1957, he worked in the biochemistry laboratory at the Ljubljana Outpatient Hospital, and from 1957 to 1979 he was employed at the Dermatology Clinic in Ljubljana as a dermatologist and as head of the biochemistry laboratory.

He passed the board exam in dermatology in 1961, and received his doctorate in 1966.

From 1965 to 1967, as a Humboldt research fellow, he underwent further training at dermatology clinics in Mainz, Frankfurt, and Munich, and he spent the 1970–71 academic year as a Fulbright scholar at Columbia University's Dermatology Department in New York.

In 1968 he was appointed to the rank of assistant professor, followed by associate professor in 1974 and full professor of dermatology in 1978.

From 1979 until his retirement in 1991, he served as head of the Dermatology Department at the School of Medicine in Zagreb.

In 1982 in Zagreb, Kansky organized the first graduate program in dermatology in the former Yugoslavia. That same year, together with his colleagues in Zagreb, he published the textbook *Kožne i spolne bolezni* (Dermatology and Venereal Diseases), which was revised and reprinted in two further editions.

In 1995, Kansky became an associate of the Department of Dermatology at the Ljubljana Medical Center, where he was responsible for teaching and research.

Kansky served as an advisor for twelve doctoral students and fifteen master's students. He published over 230 scholarly articles. As an invited lecturer, he spoke at many institutions in Europe and North America.

In 2002, together with his colleagues in Ljubljana, he published the textbook *Kožne in spolne bolezni* (Dermatology and Venereal Diseases).

He was an honorary member of the Czech and Polish dermatology societies, a member of the American Academy of Dermatology, and a corresponding member of the French, German, Aus-

trian, and Italian dermatology societies. From 1988 to 1991, he served as chairman of the Yugoslav Association of Dermatology.

In 1974, together with the late Janez Fettich and Stjepan Bunta, he founded the professional dermatology journal *Acta dermatovenereologica Jugoslavica*. He served as its editor for eight years, and as editor-in-chief from 1988 to 1991.

In 1992, Kansky founded the international dermatology journal *Acta dermatovenereologica Alpina, Pannonica et Adriatica* in Ljubljana. He was the journal's editor-in-chief until 2009, and afterwards its honorary editor.

After 1996, a combination of unfortunate circumstances placed Slovenian dermatology in a very disadvantageous position. Due to the retirement and premature death of several teaching staff, Slovenia was left without any dermatology instructors. During this period, Professor Kansky, who had already retired, was the leading Slovenian dermatologist. He organized international conferences, assisted in publication, and trained teaching and research staff, who gradually started assuming the burden that Kansky had borne alone.

In spite of his years, Aleksej Kansky remained active for a very long time. He participated in conferences, took part in graduate programs, and was present every day at the Ljubljana Department of Dermatology practically until the end of his life.

As testimony to his persistent and indefatigable work, the second revised edition of his textbook for medical and dental students, *Kožne in spolne bolezni*, was published in early 2009.

Kansky expressed a profound and accurate concept, which may serve as food for thought, when he said that "enthusiastic teachers are very important for the cultural, professional, economic, scholarly, and intellectual development of their nation, but there are differences in teachers' work. Primary- and secondary-school teachers mostly convey information to their students directly, whereas the primary task of an instructor in tertiary education is to create an appropriate environment in which they and their associates participate in teaching, research, and scholarship with pleasure. Of course, a university instructor also teaches, but those working together also learn from one another. The discipline can only advance if leaders use their professional and moral authority to lead their associates in a spirit of tolerance."

Many Slovenian physicians, especially university instructors, continue to pursue teaching and research after they retire, and they also participate in developing the profession in their area. Regrettably, we often forget them and only in rare cases is their



Maribor, 2003. Robert A. Schwartz, Jovan Miljković, and Aleksej Kansky.

work accorded the recognition and distinction it deserves!

We are grateful to Aleksej Kansky, our respected teacher and mentor, for all of the effort that he invested in the development of Slovenian dermatology. We are thankful for the great contribution that he made to molding its teaching staff, without which the advancement of modern Slovenian dermatology would not have been possible.

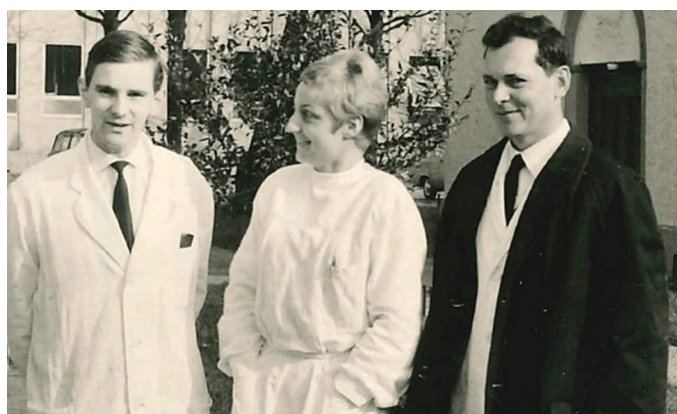
We have lost a man that enriched our time, and whose work

enriched our lives.

He will always occupy a respected place in our memory.

On behalf of the editorial board of the journal *Acta dermatovenereologica* and the Slovenian Association of Dermatology (ZSD), and also personally, I offer sincere and heartfelt condolences to the family and friends of Aleksej Kansky.

Jovan Miljković



Ljubljana, 1967. In front of the biochemistry laboratory at Dermatology Clinic in Ljubljana.



November 26th, 1982. Finishing the second semester of the first postgraduate program in dermatology.



University of Mainz ID card.



Alexander von Humboldt fellow ID card.

Abdominopelvic post-irradiation morphea in a prostate cancer patient: the first case of an under-recognized condition

Nicola di Meo¹, Cecilia Noal¹✉, Sara Trevisini¹, Bruno Ulessi¹, Giusto Trevisan¹

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To the Editor:

Post-irradiation morphea (PIM) is a rare but well-documented under-recognized complication of radiotherapy (1, 2). To our knowledge, cases of PIM after radiotherapy for prostatic carcinoma have never been reported in the literature. A 74-year-old overweight Caucasian male referred to our clinic for sclerotic cutaneous involvement of the abdominopelvic region. He reported a history of radical surgery for prostatic carcinoma (pT2a No Mo) followed by adjuvant radiotherapy (70Gy in 35 fractions) in 2010. One month earlier, an erythematous plaque had developed on the pelvic region and it gradually extended, becoming indurate, thick, and painful. He reported progressive cutaneous incarceration, with motility distress. Upon clinical examination, he presented with an indurate yellowish-white sclerotic plaque involving the upper thighs, pelvic region, and lower abdomen (Figs. 1a, b).

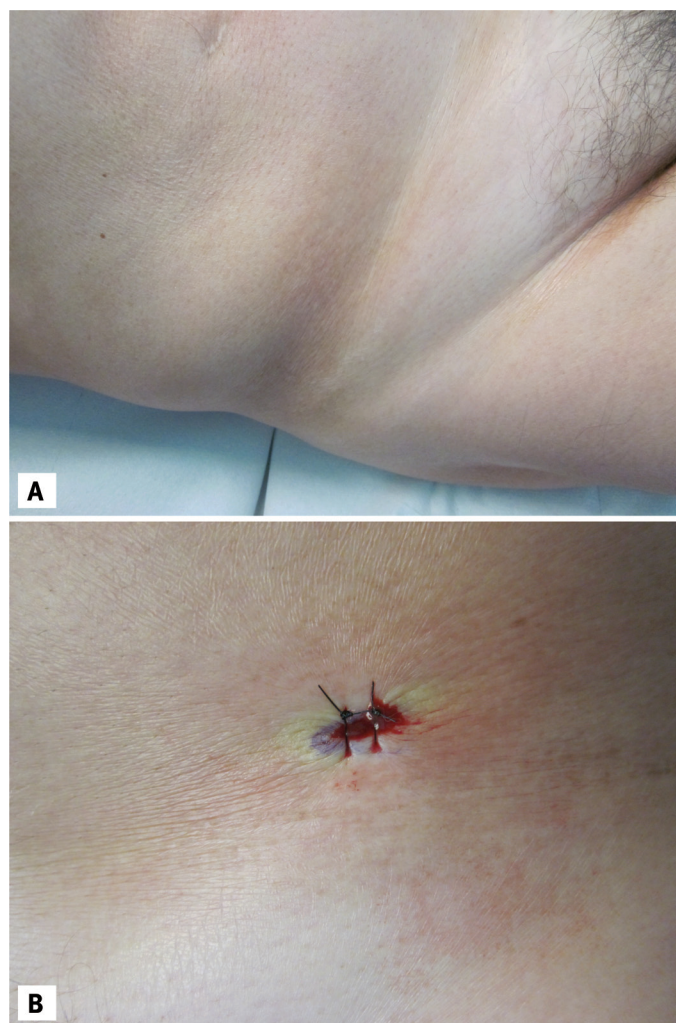


Figure 1A and 1B | An indurate yellowish-white sclerotic plaque involving the upper thighs, pelvic region, and lower abdomen.

Laboratory investigations were negative for autoantibody profile, hepatitis, and *Borrelia burgdorferi*. Histological examination revealed a lymphocytic infiltration of the reticular dermis with plasma cells (Fig. 2). Clinical and instrumental exams did not reveal any relapse of cancer or metastatic disease. Because of his anamnesis, clinical findings, and histological features, a diagnosis of PIM was made. The patient started therapy with UVA1 phototherapy associated with daily topical calcipotriol. Clinical improvement was achieved after 3 months, with a mild softening of the skin involved.

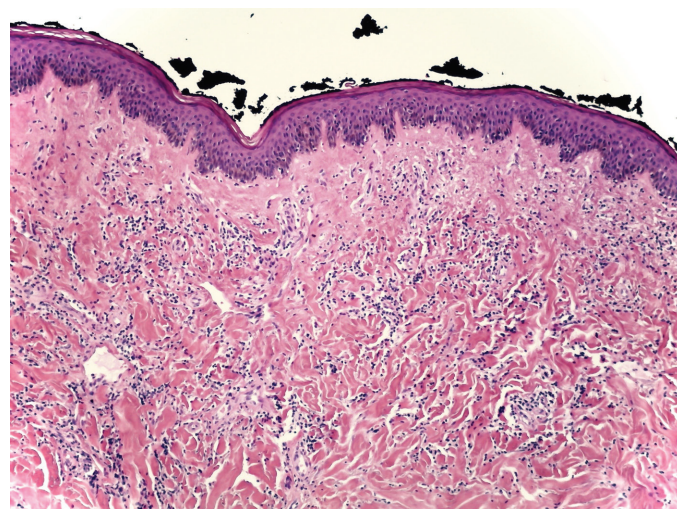


Figure 2 | Lymphocytic infiltration of reticular dermis with plasma cells.

Post-irradiation morphea (PIM) is a rare skin complication of radiotherapy. In a previous study, the incidence of localized morphea following radiotherapy appears to be approximately two out of every 1,000 patients (3). It can occur 1 to 12 months after radiation, and as much as 32 years later. PIM is more frequent in female patients; there has been only one case in a male with subcutaneous lymphoma (4). The majority of PIM occurs in patients treated for breast carcinoma. It is a less common complication after neoadjuvant radiotherapy for head and neck cancer, endometrial cancer, and gastrointestinal neoplasia (5). PIM is characterized by sclerotic plaque, erythema, and induration. Usually it is restricted within the radiation area, but in the literature PIM is reported to extend beyond the irradiated area or involve a distant site (6–7). PIM often presents a difficult diagnosis, especially in non-classical presentations. Radiation-induced fibrosis (RIF), radiation recall dermatitis, post-irradiation sclerodermatous panniculitis, and cancerous sclerosing recurrence are the main differential diagnoses. Skin biopsy results are helpful for distinguishing the disease. PIM occurs later in relation to radiotherapy compared to RIF, which usually appears in the first 3 months. There is usually

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an abrupt onset in PIM, with an initial erythema and thickening that is not observed in RIF (4). Histological findings demonstrated dermal inflammatory infiltrates, which are absent in RIF. Radiation recall dermatitis has been defined as the skin "recalling" previous radiation exposure in response to the administration of drugs (8). The post-irradiation sclerodermatous panniculitis histological pattern reveals significant changes in the subcutaneous tissues with lobular panniculitis. The dermis is nearly unaffected (9).

Treatment of post-irradiation morphea is difficult, and many cases are recalcitrant to therapy. Topical and intralesional corticosteroids, oral and systemic antibiotics, topical hyaluronidase and methotrexate, and chloroquine are used in PIM (10). In some patients, a spontaneous gradual softening of the skin could be observed. In the literature, several studies reported the effectiveness of a combined treatment of calcipotriol and UVA1 irradiation to treat morphea (11). The pathogenesis is still unknown. Davis et al. proposed that radiotherapy induces neoantigen formation, which starts a T-cell response months to years after exposure, stimulating the production of transforming growth factor (TGF- β). TGF- β induces fibroblast activation and the production of extracellular

matrix proteins, and inhibits the degradation of matrix proteins, implying extensive fibrosis (12). Hermann et al. suggest that there is a higher secretion of Th2 cytokines (interleukin 4, interleukin 5), which stimulate collagen synthesis (13). Another theory explains the development of PIM due to a premature terminal differentiation of fibroblast to myofibroblast (14). There seem to be no clear predictive factors predicting the development of PIM. Radiotherapy total dose, age of the patient, dose per fraction, acute skin side effects, or history of autoimmune diseases appear not to be important risk factors (10). Breast size seems to play a role in the development of PIM, perhaps because large breasts have a higher fat content or the radiotherapy dose is inhomogeneous (15). Similar anatomical conditions can be detected in an overweight patient, as in our case. PIM is a rare complication with important adverse side effects of radiotherapy. In the literature, PIM has mainly been described in females treated for breast cancer and it extends within the irradiated area. Considering the amount of radiotherapy for prostate cancer since its introduction, it is possible that our case is the first case of an under-recognized condition.

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Ecthyma gangrenosum versus ecthyma-like lesions: should we separate these conditions?

Michael Vaiman^{1✉}, Tsilia Lasarovitch², Lior Heller³, Gad Lotan⁴

Abstract

Introduction: We analyzed cases of ecthyma gangrenosum (EG) and “ecthyma-like” or “ecthyma-mimicking” cases of necrotic lesions of the skin to improve current definitions of these conditions.

Methods: The retrospective analysis compared 28 cases of lesions (from 2001 to June 2015) that were identified as EG. Age, sex, lesion location, time from macule to ulcer, underlying diseases, number of lesions per patient, wound bacterial culture, blood culture, and immune status served as variables for analysis and comparison.

Results: Only in 20 cases (71.42%) was *Pseudomonas aeruginosa* the etiology of the lesion. The etiology of eight cases was various bacterial species (five cases, 17.85%) and fungal species (three cases, 10.73%). In 21 cases (75%), the lesion appeared in immunocompromised patients. In four cases (14.28%), the patients suffered from *Pseudomonas* sepsis. In four cases (14.28%), the lesion appeared in healthy individuals. There was no difference in clinical picture, lesion location, number of lesions per person, and treatment strategy between *Pseudomonas* and non-*Pseudomonas* cases.

Conclusions: Necrotic lesions resembling EG can have various microbiological etiology and can occur in immunocompetent or healthy persons. With no difference in clinical picture, two separate definitions should not be applied to *Pseudomonas* and non-*Pseudomonas* cases. We suggest accepting a broader definition of EG.

Keywords: ecthyma gangrenosum, ecthyma-like lesions, necrotic lesion, *Pseudomonas aeruginosa*

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Introduction

Ecthyma gangrenosum (EG) is a relatively uncommon condition. It has been known since 1897 and the term itself was generally accepted in the 1950s (1, 2). Until the 1970s, it was thought that this condition was pathognomonic of *Pseudomonas* septicemia (*Pseudomonas aeruginosa*) and that it should usually be seen in immunocompromised patients, particularly those with underlying malignant disease (3, 4). Since the 1980s, it has been understood that various bacteria such as *E. coli*, *Citrobacter freundii*, *Klebsiella pneumoniae*, various other *Pseudomonas* species, and *Morganella morganii* may be etiologic agents for EG as well as some fungi (*Candida albicans* and others) (5–7). The infection is not necessarily a monoculture and, for example, *Candida albicans* can coexist with *Pseudomonas aeruginosa* in the same lesion (7). To make matters worse, it was then reported that EG is not specific to immunocompromised patients but can also manifest in immunocompetent patients as well (8). Finally, it was reported that EG can affect an otherwise healthy person, and the entire concept that EG is a skin manifestation of severe systemic infection was called into question (9). Cases of EG diagnosed in healthy newborn infants exacerbated this confusion (10, 11).

Although they are generally accepted, the exact clinical manifestations also have unanswered questions. For example, most authors agree that the skin lesions usually occur in the gluteal and perineal regions (57%) or extremities (30%) (12, 13). At the same time, the lesions may appear on the face, chest, arms, neck—in fact, all over the body (9, 14). Thus, currently we have no detailed knowledge about this condition. Some authors have tried

to overcome this confusion by suggesting two definitions: EG and EG-like lesions (11, 15, 16), or “mimicking ecthyma gangrenosum” lesions (17).

What is definitely known is that the skin lesion begins as an erythematous nodule or hemorrhagic vesicle, which evolves into a necrotic ulcer with an eschar (4–7). An early lesion may transform into a necrotic ulcer in as little as 12 hours. The skin lesions can be single or widespread over the body, and the case fatality rate is high. If patients with EG are immunocompromised, they are usually suffering from leukemia, lymphoma, other malignant diseases, severe burns, or organ transplant, or might be receiving immunosuppressive therapy (18–20). Blood cultures and skin biopsy with culture are necessary for precise diagnosis. A second skin biopsy is usually sent for tissue culture for bacteria, fungi, yeasts, and mycobacteria. Sensitivity tests are carried out on any isolated organisms. When the etiology is established, aggressive antibiotic or anti-fungal treatment is prescribed but, because EG manifests as a necrotizing soft-tissue lesion, surgical excision is often necessary. The surgeries vary from aggressive surgical debridement and skin grafting to relatively mild plastic surgeries.

The purpose of the current research was to seek to give some order to the current situation with EG and answer whether “EG-like lesion” should be accepted as a separate definition.

Materials and methods

The methodology of the research was based on a comparative analysis between our own EG cases and cases described in the literature with respect to etiology, underlying diseases, immune status,

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and location of the lesions. A retrospective cohort study reviewed the medical records of patients with EG that were admitted to the Emergency Department and referred to the Surgical Department or Dermatology Department at the Assaf Harofeh Medical Center from January 2001 to June 2014. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected a priori after approval by the institution's Helsinki committee.

Inclusion/exclusion criteria were as follows: tissue defects due to burns were excluded from the analysis. All other cases with an EG-specific tissue defect that were admitted and had signs of general and/or local infection and skin necrosis were included, whatever etiology was detected. The presence or absence of underlying diseases such as malignancy, specific infectious disease, connective tissue disease, diabetes, AIDS, and other immunocompromising pathologies were taken into account. In all of the cases analyzed, a differential diagnosis was performed between EG and Warfarin-induced skin necrosis, cocaine-induced skin necrosis, calciphylaxis, septic emboli, loxoscelism, diabetic microangiopathy, disseminated intravascular coagulation, necrotizing vasculitis, paraneoplastic extensive necrotizing vasculitis, pyoderma gangrenosum, livedoid vasculopathy, necrotizing fasciitis, and necrosis secondary to the use of vasoactive drugs. If the records lacked complete information on these subjects, the cases were excluded from the analysis. Records with incomplete or unclear bacteriological results were excluded from the analysis.

Results

Twenty-eight cases were identified following the inclusion/exclusion criteria. The flow was as follows: out of 49 cases, 16 were excluded because of lack of complete data on differential diagnosis, and five cases were excluded because of a lack of clear bacteriological data. All of the patients had previously untreated EG lesions. All of the patients received standard lesion inspection/sanitation/closure procedures at the Emergency Department and were then referred to the Dermatology Department, of them 23 patients (82%) with further reference to surgery. General data on the cases are presented in Table 1.

Bacteriological results, clinical picture, and treatment results were obtained for each case. On the 1st or 2nd day after admission, the blood culture and culture specimen from the skin lesion were obtained. In all identified cases, bacteriological samples were processed in the hospital's laboratory department. Specimen processing included detection of bacteria by culturing, biochemical identification, and susceptibility testing. Specimens were inoculated into the following culture media: MacConkey agar and blood agar. Cultured plates were examined after overnight incubation at 37 °C; if no growth was obtained in the plates, they were re-incubated for another 24 hours. Identification of *Pseudomonas aeruginosa* and an antibiotics susceptibility test were performed using VITEK 2 instrument, bioMérieux, according to CLSI (Clinical Laboratory Standards Institute) interpretive standards. The bacteriological data are presented in Table 2.

In 20 cases (71.42%), *Pseudomonas aeruginosa* was the etiology of the lesion. The etiology of eight cases was various bacterial species (five cases, 17.85%) and fungal species (three cases, 10.73%). In 21 cases (75%), the lesion appeared in immunocompromised patients. Only in four cases (14.28%) did the patients suffer from *Pseudomonas* sepsis. In four cases (14.28%), the lesion appeared in healthy individuals. There was no difference in clinical picture, lesion location, number of lesions per person, and treatment strategy between *Pseudomonas* and non-*Pseudomonas* cases.

Table 1 | General data on 28 observed cases of ecthyma gangrenosum.

Case no.	Age	Sex	Lesion location	Macule to ulcer	Diseases	No. of lesions
1	5	M	arm	in 12 hours	leukemia	single
2	18	M	buttock	in 18 hours	healthy	single
3	54	M	buttock, leg	in 2 days	rheumatoid arthritis	multiple
4	38	F	face	in 2 days	multinodular goiter	single
5	33	F	back, leg	in 1.5 days	cancer treatment	multiple
6	12	F	forearm	in 12 hours	leukemia	single
7	87	M	back	in 2 days	cancer treatment	single
8	65	F	leg	in 3 days	diabetes mellitus	single
9	52	M	buttock	in 2 days	cancer treatment	single
10	43	M	leg	in 24 hours	leukemia	single
11	19	F	leg	in 24 hours	rheumatoid arthritis	single
12	45	F	buttock	in 1.5 days	leukemia	single
13	45	F	leg	in 3 days	cancer treatment	single
14	38	F	back	in 24 hours	healthy	single
15	29	M	buttock	in 2 days	cancer treatment	single
16	74	M	back, leg, foot	in 2 days	cancer treatment	multiple
17	69	M	face	in 5 days	lymphoma	single
18	7	F	leg, arm	in 24 hours	leukemia	multiple
19	24	M	chest	in 24 hours	rheumatoid arthritis	single
20	83	M	leg	in 24 hours	cancer treatment	single
21	65	F	leg	in 2 days	cancer treatment	single
22	66	M	abdomen	in 4 days	lymphoma	single
23	38	M	leg	in 7 days	leukemia	single
24	44	F	back	in 24 hours	abscess	single
25	71	F	buttock, leg	in 24 hours	leukemia	multiple
26	57	F	face	in 2 days	healthy	single
27	18	M	buttock	in 24 hours	leukemia	single
28	53	M	buttock	in 2 days	healthy	single

Table 2 | Microbiology lab data on 28 observed cases of ecthyma gangrenosum.

Case no.	Age	Culture in wound	Culture in blood	Immunocompromised?
1	5	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	Yes, leukemia
2	18	<i>P. aeruginosa</i>	none	No
3	54	<i>P. aeruginosa</i>	none	Yes, rheumatoid arthritis
4	38	<i>P. aeruginosa</i>	none	No
5	33	<i>A. hydrophila</i>	none	Yes, cancer treatment
6	12	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	Yes, leukemia
7	87	<i>P. aeruginosa</i>	none	Yes, cancer treatment
8	65	<i>P. aeruginosa</i>	none	No
9	52	<i>A. hydrophila</i>	none	Yes, cancer treatment
10	43	<i>P. aeruginosa</i>	none	Yes, leukemia
11	19	<i>P. aeruginosa</i>	none	Yes, rheumatoid arthritis
12	45	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	Yes, leukemia
13	45	<i>P. aeruginosa</i>	none	Yes, cancer treatment
14	38	<i>P. aeruginosa</i>	none	No
15	29	<i>Fusarium solani</i>	none	Yes, cancer treatment
16	74	<i>P. aeruginosa</i>	none	Yes, cancer treatment
17	69	<i>Candida albicans</i>	none	Yes, lymphoma
18	7	<i>P. aeruginosa</i>	none	Yes, leukemia
19	24	<i>P. aeruginosa</i>	none	Yes, rheumatoid arthritis
20	83	<i>P. aeruginosa</i>	none	Yes, cancer treatment
21	65	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	Yes, cancer treatment
22	66	<i>P. aeruginosa</i>	none	Yes, lymphoma
23	38	<i>P. stutzeri</i>	none	Yes, leukemia
24	44	<i>P. aeruginosa</i>	none	No
25	71	<i>E. coli</i>	none	Yes, leukemia
26	57	<i>A. hydrophila</i>	none	No
27	18	<i>Fusarium solani</i>	none	Yes, leukemia
28	53	<i>P. aeruginosa</i>	none	No

In 18 cases, the buttocks and/or lower extremities were affected (64.5%), but the rest of the ten cases presented lesions in various parts of the body, including the face (three cases, 10.7%).

During the period from 2001 to 2014, empiric antibiotic therapy experienced some changes. Ceftazidime, ampicillin, and conventional amphotericin B were used more often. Specific therapy was administered upon availability of results from the microbiology department. There was no uniformity in these results. For

example, 10 isolates (50% of *P. aeruginosa* cases) were resistant to ceftazidime, and another 10 isolates (50%) were resistant to ampicillin but susceptible to ceftazidime. Following bacteriological results, the antibiotic treatment was changed to gentamicin (two cases), ampicillin (10 cases), ceftazidime (one case), ciprofloxacin (two cases), doxorubicin + vincristine (one case), ceftazidime (three cases), and clindamycin + ciprofloxacin (two cases) that were administered as standard protocols require. Standard wound care included wet to dry dressing changes.

As for non-*Pseudomonas* cases, *Aeromonas hydrophila* (three cases) had different antibiotic sensitivities and were treated with cephalosporin. The case caused by *Pseudomonas stutzeri* was successfully treated with chlorhexidine. *Escherichia coli* (one case) was sensitive to ampicillin. Two cases due to *Fusarium solani* were treated with local debridement and topical amphotericin B. Another fungal case, in which *Candida albicans* was involved, was successfully treated with amphotericin B and caspofungin.

In 23 cases (82.14%), various surgical treatment was needed, mainly surgical debridement (in all 23 cases) followed by minor plastic surgery in five cases (17.85%). In two cases, both on the back, the lesions were more than 10 cm in diameter and skin grafting was performed. Among these 23 surgical cases, acute inflammatory cell infiltration and vascular proliferation were seen in the dermis in 17 cases, but in six cases the process also involved the subcutaneous tissue. The surgical approach to *Pseudomonas* and non-*Pseudomonas* cases was similar.

The treatment of EG was successful in all 28 cases in our series, but five patients died afterwards because of their main diseases.

Discussion

The generally accepted definition of EG states that this condition is a bacterial skin infection usually caused by *Pseudomonas aeruginosa*, which appears in the context of *P. aeruginosa* sepsis in immunocompromised patients (2–4, 18, 21). When it was understood that *P. aeruginosa* is not the only etiological agent for EG, an attempt was made to separate “real” EG from “EG-like” or “EG-mimicking” lesions. At that point, the first definition was applied to *P. aeruginosa* EG cases and the second definition to all EG cases of different etiology. The term “nonpseudomonal ecthyma gangrenosum” was also suggested (22).

As stated in the introduction, continuous description of EG cases of various etiology, in immunocompetent and even healthy individuals, started in the 1960s and 1970s. The majority of these descriptions are presented as case reports and number of these reports is growing every year. The recently published review on EG literature indicates that *P. aeruginosa* was detected in 73.65% of cases; of them, there were only 72 cases (58.5%) with sepsis (23).

Comparing our series of cases with the cases that have been described in the literature, we did not find any clinical difference between *Pseudomonas* and non-*Pseudomonas* EG cases. To illustrate our point, we present two cases (Figs. 1 and 2). In both cases, the face was affected at approximately the same location. Some case reports state that EG is extremely rare in the face, but in fact it is not so rare. In the first case (case 4, 38, F), *P. aeruginosa* was the etiology of the lesion. In the second case (case 17, 69, M), *Candida albicans* caused similar skin necrosis. Both cases were successfully treated by the same protocol, which is indicated below.

If an etiological approach is warranted, one can define *Pseudomonas* EG, other-bacteria EG, fungal EG, and so on. Clinically, one sees the same disorder. If a clinical approach is warranted, the conditions should not be separated on the basis of possible



Figure 1 | A case of facial EG (case 4, 38, F) with *P. aeruginosa* as the etiology of the lesion.



Figure 2 | A case of facial EG (case 17, 69, M) with *Candida albicans* as the etiology of the lesion.

microbiological causes that vary broadly. EG is a reaction pattern of the skin to compromised local blood flow, and this reaction generally occurs irrespective of the bacterial or non-bacterial agent. In all cases, whatever the etiology is, the protocol to manage a patient remains the same:

1. Recognize the necrotic skin lesion as EG, perform differential diagnosis;
2. Send samples for bacteriological investigation;
3. Administer empiric antibiotic therapy;
4. Obtain results from the microbiology department;
5. Change the antibiotic or antifungal treatment accordingly;
6. Apply surgery as needed.

A Wood's lamp (Wood's light, black lamp) can be used to speed up this process. By using this diagnostic tool, a physician can see the green fluorescence if there is *Pseudomonas aeruginosa*, allow-

ing proper antibiotic therapy before culture results are obtained from the laboratory (24, 25).

In our series, we had numerous variations of the disorder: EG due to *P. aeruginosa* in an immunocompromised patient (cases 1, 3, 6, 10, 11, etc.), EG due to *P. aeruginosa* in an immunocompetent patient (cases 2, 4, 8, etc.), EG due to *P. aeruginosa* in a healthy patient (cases 14, 28), EG due to various bacterial infection in an immunocompromised patient (cases 5, 9, 23, 25), and fungal EG (cases 15, 17, 27). We observed cases with and without septicemia. *P. aeruginosa* etiology and immunocompromised status prevailed, but were not obligatory.

Any attempt to change the definition is open to further discussion. Analyzing our experience and reports in the emerging literature, we suggest defining EG as a bacterial skin infection of various etiology that leads to vasculitis and further local skin ne-

crosis. The disorder is more likely to appear in the presence of *P. aeruginosa* and immunocompromised status of a patient. However, only a minority of patients are septic and other organisms can be associated with ecthyma-like lesions.

Conclusion

Necrotic lesions resembling ecthyma gangrenosum can have various microbiological etiology, and can occur in immunocompetent or even healthy persons. Although there is no difference in the clinical picture, we do not think that two separate definitions should be applied to *Pseudomonas* and non-*Pseudomonas* cases. Instead, we suggest accepting a broader definition of ecthyma gangrenosum.

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Plasma-soluble urokinase plasminogen activator receptor (suPAR) levels in psoriasis patients and correlation with disease severity

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Abstract

Objective: Psoriasis is a chronic, relapsing, inflammatory, hyper-proliferative skin disease. Plasma-soluble urokinase plasminogen activator receptor (suPAR) is released from the cell membrane-bound plasminogen activator and is a new biomarker of systemic inflammation. The aim of this study is to investigate plasma levels in psoriasis patients and determine their correlation with the Psoriasis Area and Severity Index (PASI) score.

Materials and methods: The plasma suPAR levels of 50 healthy individuals and 65 psoriasis patients were measured using the Micro-ELISA method and the relation with PASI was investigated.

Results: On comparing plasma suPAR levels of the psoriasis patients with the control group consisting of healthy individuals, no statistically significant difference was determined ($5.29 \text{ ng/ml} \pm 2.12$ and $6.03 \text{ ng/ml} \pm 2.42$, respectively, $p = 0.326$; Table 1). Likewise, there was no significant correlation between the suPAR levels and PASI score ($r = 0.147$, $p = 0.243 > 0.05$).

Conclusions: There was no statistically significant difference in the plasma suPAR levels of psoriasis patients compared to the control group. Nevertheless, we firmly believe that plasma suPAR, a new biomarker, could indicate disease severity if conducted with larger patient series and with moderate to severe psoriasis patients.

Keywords: psoriasis, suPAR, PASI

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Introduction

Psoriasis is a hereditary polygenic chronic and recurrent inflammatory skin disease with a multifactorial etiology. The disease, with a genetic predisposition, is considered to emerge due to the impact of infections and environmental factors such as emotional stress and trauma with T-cell-mediated immune mechanisms (1–3). Currently there is no laboratory indicator indicating disease activity and making possible the comparison of treatment modalities in psoriasis.

Soluble urokinase plasminogen activator receptor (suPAR) is a glycosylphosphatidylinositol (GPI) membrane protein bound to a urokinase-type plasminogen activator receptor (uPAR) in soluble form. An increase in immune system activation will lead to elevated serum suPAR levels (4). In recent years, it has been defined as a valuable indicator of immune system activation. Elevated suPAR levels have been widely demonstrated in several studies on inflammatory diseases and cancer (5–8).

The aim of this study is to analyze plasma suPAR levels of psoriasis patients and determine whether there is a possible relation to disease intensity.

Materials and methods

The participants in this study were 65 patients diagnosed with clinical and histopathological psoriasis, 35 (53%) female and 30 male (46.2%), and 50 healthy individuals (25 female and 25 male).

Subsequent to Selçuk University Faculty of Medicine Ethics Committee approval, the study was conducted from January 2013 to July 2013. Informed consent was obtained from all participants

in this study. Patients that underwent systemic, topical anti-psoriatic, and/or photo (chemo) therapy within the previous four weeks were excluded from the study. Patients with hypertension, diabetes mellitus, chronic renal failure, liver disease, heart failure, acute or chronic infection, accompanied autoimmune disease, and malignancy were also excluded.

Socio-demographic information for all participants was recorded, and the psoriasis area severity index (PASI) was used to calculate disease severity.

Five ml of venous blood was taken at 8:00 am from the patient and control groups. Peripheral venous blood samples were obtained using EDTA-containing blood collector tubes and plasma samples through centrifuging. Plasma samples were stored deep frozen at -80°C until suPAR levels were measured. suPAR assays were evaluated using a micro ELISA reactive receptor (PLAUR / uPAR) ELISA Kit, Hangzhou East Biopharm Co. Ltd. Hangzhou, PRC and microplate reader (BiotekELx 800, BioTek Instrumentations, Inc., Winooski, VT, USA).

During the statistical analysis, the Mann–Whitney U test was used for two independent groups with normal distribution, and for abnormal distribution Spearman's rho correlation coefficient was used. As a statistical significance threshold, the level $p < 0.05$ was accepted.

Results

Out of the 65 psoriasis patients, 35 (53.8%) were female and 30 (46.2%) male. The control group, 50 in total, consisted of 25 (50.0%) healthy female and 25 (50.0%) healthy male participants. The mean age of the psoriasis patients was 36.17 ± 13.93 years and

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of the control group 33.82 ± 13.16 years. There was no statistically significant difference in terms of age and sex between the groups ($p > 0.05$). In the psoriasis patient group, 42 (64.6%) cases had plaque-type psoriasis and 23 (35.4%) guttate psoriasis. The mean PASI score of the patient group was 11.3 ± 7.8 and mean disease duration 11.1 ± 11.5 years. No statistically significant difference was seen on comparing patient and control-group plasma suPAR levels (5.29 ± 2.12 ng/ml and 6.03 ± 2.41 ng/ml, respectively, $p = 0.326 > 0.05$; Table 1). Likewise, there was no statistically significant correlation between plasma suPAR levels and PASI scores ($r = 0.147$, $p = 0.243 > 0.05$). No statistically significant difference was seen in terms of disease duration (> 10 and < 10 years) and mean suPAR levels ($p = 0.890$; Table 2). In terms of sex in the psoriasis group, there was no statistically significant difference in the suPAR levels ($p = 0.114$; Table 3).

Table 1 | Plasma suPAR levels in psoriasis and control groups.

	suPAR (pg/mL)	P value
Psoriasis	5.29 ± 2.12	0.326
Control	6.03 ± 2.41	

$P > 0.05$

Table 2 | Plasma suPAR levels by mean duration in the psoriasis group.

Psoriasis duration	n	suPAR (ng/mL)	P value
< 10 years	31	5.29 ± 2.36	0.890
> 10 years	34	5.3 ± 2.16	

$P > 0.05$

Table 3 | Plasma suPAR levels by sex.

Sex	n	suPAR (ng/mL)	P value
Female	35	5.75 ± 1.91	0.114
Male	30	4.98 ± 2.26	

Discussion

To the best of our knowledge, this study is the first to investigate suPAR levels in psoriasis patients. Compared to the control group, the plasma suPAR levels of psoriasis patients revealed no statistically significant difference. These outcomes might be attributed to the fact that the psoriasis patients had mild to moderate levels of disease severity in this study.

Urokinase-type plasminogen activator receptor (uPAR) contains three fields and is present in monocytes, activated-T lymphocytes, macrophages, endothelial cells, keratinocytes, fibroblasts, smooth muscle cells, megakaryocytes, and certain tumor cells. suPAR divides itself from membrane-bound uPAR and, depending on the immunity activation, is present in various concentrations in the plasma, urine, blood, and serum fluid (9–11). Hence, increased immune system activation leads to elevated suPAR serum levels. The same has been reported in a variety of pathological conditions, including paroxysmal nocturnal hemoglobinuria, human immunodeficiency virus type-1 (HIV-1) infection, malaria, pneumococcal and streptococcus pneumonia bacteremia, sepsis, bacterial and viral central nerve system (CNS) infection, active tuberculosis (TB), and even various solid tumor forms (12–17).

Many experimental studies have determined increased suPAR

systemic levels in cancer as well as in various infectious and inflammatory diseases. Among the infectious and inflammatory diseases are human immunodeficiency virus (HIV), malaria, tuberculosis, central nervous system infections, urinary tract infections, arthritis, liver fibrosis, and inflammatory bowel disease (18–23).

Systemic levels of suPAR were found to be a strong prognostic value in HIV-infected individuals. In addition, it is of prognostic value in predicting the course and severity of cancer patients (24).

Likewise, quite high systemic suPAR levels have been determined in critical and serious diseases such as sepsis, systemic inflammatory response syndrome, or bacteremia and are of disease-prognostic value (25–26).

Enocsson et al. studied the plasma suPAR levels of 198 systemic lupus erythematosus (SLE) patients and determined significantly elevated suPAR levels compared to the healthy control group. At the same time, they determined a strong association between systemic suPAR levels and organ damage (27).

Another study on 89 SLE patients carried out by Toldi et al. also determined higher suPAR serum levels compared to the control group and claimed that this can be used as a marker to determine patients with high disease activity (28).

In a study by Kasperske-Zajac et al. examining patients with atopic eczema / dermatitis syndrome (AEDS), the uPA and suPAR levels of moderate and severe AEDS patients did not differ from those of healthy controls (29).

Psoriasis is a chronic, relapsing, inflammatory, and hyper-proliferate skin disease with an unclear etiology. Parameters showing the inflammatory process activation in order to follow the clinical course and to develop treatment strategies are important (30–31). Currently, there are no widely recognized laboratory markers determining disease activity.

To the best of our knowledge, there are no studies investigating suPAR levels in psoriasis patients.

Despite the reports on elevated systemic suPAR levels in various inflammatory diseases, in this study there was not a statistically significant difference in the plasma suPAR levels of psoriasis patients and the healthy control group. Likewise, a statistically significant correlation between plasma suPAR levels and PASI scores in psoriasis patients could not be detected. The underlying reason might be that the study group consisted of mild- to moderate-level psoriasis patients.

Conclusion

suPAR levels, a potential useful biomarker in demonstrating disease severity and risks of possible comorbidities in future, must be further researched with larger patient series and in psoriasis patients with higher PASI scores.

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Parry–Romberg syndrome: a case with a possible association with Lyme disease

Nicola di Meo¹, Giuseppe Stinco², Katuscia Nan¹✉, Caterina Pinzani², Giusto Trevisan¹

Abstract

Parry–Romberg syndrome is an acquired slowly progressive disease characterized by an atrophy mostly involving half of the face. The pathogenesis of this disfiguring condition is still controversial. The relationship between Parry–Romberg syndrome and Lyme disease needs to be considered in depth. A 16-year-old woman from Albania presented with linear depressions of the right side of the face, clinically compatible with Parry–Romberg syndrome. She had a positive history of Lyme disease. *Borrelia* infection was confirmed by the positivity of PCR and the presence of IgM antibodies. The patient received intravenous penicillin and metronidazole for 14 days. After treatment and during a 2-year follow-up, the clinical disease progression was halted and the serological and microbiological tests for *Borrelia burgdorferi* sensu lato were negative. We cannot exclude a coincidence, however, of the bacteriological and serological evidence. Moreover, the interruption of the disease progression after the antibiotic therapy is difficult to ignore without claiming that this association is at least suggestive.

Keywords: Parry-Romberg Lyme disease, borreliosis, *Borrelia*, morphea

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Introduction

Parry–Romberg syndrome is an uncommon acquired slowly progressive hemifacial atrophy of unknown etiology that also rarely involves the ipsilateral part of the limbs (1). This syndrome has many features of linear scleroderma “en coup de sabre,” but it is characterized by more extensive involvement of the lower face with only a slight cutaneous sclerosis (2). It is due to gradual wasting of the subcutaneous fat, accompanied by an atrophy of the skin and, infrequently, of the muscles and bones. In particular, bone and cartilage tissues are rarely affected, unless the onset occurs before the second decade, when the face and skull structures are not fully developed (2). The average onset of this disease is in the first two decades, beginning with a progressive phase that may span up to 20 years and thereafter tending toward stabilization (1). In 15% of the cases, neurological signs and symptoms such as trigeminal neuralgia, facial paresthesia, headache, and focal epilepsy are present (1). The pathogenesis of this syndrome remains unexplained: it is thought to be a unilateral inflammatory process associated with a chronic vascular or neurogenic disturbance such as sympathetic dysfunction (3). Other postulated causes include autoimmunity, inheritance, local trauma, focal scleroderma, endocrine and metabolic disorders, and other factors, including *Borrelia burgdorferi* sensu lato infections (1–4). The role of *Borrelia burgdorferi* sensu lato in the development of atrophosclerodermic diseases is well known even when the facial area is involved (5–7). In the literature there are few reports showing the association between Parry–Romberg syndrome and borreliosis (2, 8–11). We present another case of Parry–Romberg syndrome in which the correlation with *Borrelia burgdorferi* infection could be strongly suspected.

Case report

A 16-year-old woman from Albania presented with linear depres-

sions of the right side of the face, clinically compatible with Parry–Romberg syndrome. She developed a progressive facial right asymmetry from the age of 11 and had no memory of any significant local trauma and no family history of progressive hemifacial atrophy or similar conditions. Dermatological examination revealed a linear atrophic depression of soft tissues, especially of the lower part of the right cheek and of the right side of the chin with labial asymmetry and tongue hemiatrophy. No eyebrow or forehead alopecia was present (Fig 1). There was no evidence of sensory or motor functional deficits on either side. Lyme ELISA (NovaTec Immunodiagnostica GmbH) IgM antibodies (antigens: Flagellin recombinant and purified OspC) were elevated in serum (178 UA/ml, normal values < 24 UA/ml), whereas IgG were normal. The IgM positivity was confirmed by immunoblot test (NovaTec Immunodiagnostica GmbH): 24 kDa(OspC), 41 kDa(Fla), 39 kDa(p39). The patient remembered a tick bite 5 to 6 years earlier in the upper right area of the neck, close to the subsequent atrophic area, with a history of a retarded surrounding erythema, spontaneously resolved, most likely attributable to an erythema chronicum migrans. At that time she was not tested. A complete blood cell count, chemistry panel, and lipid profile revealed unremarkable findings. Serum and urine protein electrophoresis tests produced normal results, as did liver-, renal-, and thyroid-function tests, erythrocyte sedimentation rate, C-reactive protein level, antinuclear antibodies, human immunodeficiency virus antibodies, hepatitis B and C surface antigens, and VDRL test. Only a low count of CD57+ natural killer cells was present. Polymerase chain reaction real time (RT-PCR) assay for *Borrelia burgdorferi* sensu lato detection, performed on DNA obtained from peripheral blood, was positive. The patient refused a new biopsy on her face in order to perform a culture of *Borrelia burgdorferi* sensu lato. All subcutaneous structures were intact: an X-ray of the facial mass showed that the two halves of the facial skeleton were symmetrical and regularly developed. No consistent central and peripheral nervous system disorder was noticed, neither based on patient

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history or physical and electrographic examination (EEG), nor based on the quality of cerebrospinal fluid (colorless, with a negative Pandy reaction and with glucose, electrolytes, and proteins in the normal range) and on neuroimaging (brain and brainstem SPECT and MRI). In line with serological positivity for Lyme disease, the patient underwent an intravenous antibiotic treatment with intravenous penicillin G at a dosage of 20 million units per day associated with intravenous metronidazole (500 mg daily) for 14 days. After 6 months, the IgM antibodies were 89 UA/ml, with the same immunoblot panel and blood PCR negative. After 14 months, the IgM antibodies were 36 UA/ml, the IgM immunoblot was positive for p39 and p41, and blood PCR was negative. After 24 months, the clinical disease progression had definitely halted and IgM antibodies as well as blood PCR for *Borrelia burgdorferi* sensu lato were negative. In order to correct the residual facial asymmetry and reshape the facial contour, a liposuction session was carried out (Fig. 2).

Discussion

Since the first description of Parry–Romberg syndrome in 1825, this syndrome has aroused questions and reflection about its pathogenesis. It is not yet well known and seems to be heterogeneous, including trauma, infection, heredity, vascular malformation, auto-immunity, endocrine disturbances, disturbance of fat metabolism, and sympathetic dysfunction (12). Although the relationship of *Borrelia burgdorferi* sensu lato infection to Par-

ry–Romberg syndrome has occasionally been reported, the role of *Borrelia burgdorferi* sensu lato in the development of Parry–Romberg syndrome is uncertain (2, 8–14). In a retrospective study on 12 patients with progressive facial atrophy, Sommer et al. (14) reported no association of both disorders. In contrast, our case indicates that there is strong evidence that *Borrelia burgdorferi* sensu lato infection is related to Parry–Romberg syndrome. Progressive facial hemiatrophy began when the woman was only 11 years old. She recalled a previous history of an annular lesion, likely an erythema chronicum migrans, that appeared after a tick bite. No information is available on whether antibiotic treatment was offered. Her serology for Lyme disease was positive, although only for IgM. OspC and p39 are proteins highly specific for *Borrelia burgdorferi* sensu lato. P41 is specific for the various *Borrelia* species of the same genus. *Borrelia burgdorferi* sensu lato-specific gene segments by real-time blood PCR were detected (using a locally developed method that amplifies a fragment of flagellin gene). The decrease in the CD57 lymphocyte subset may be a marker of Lyme disease (15). After the antibiotic therapy, we noticed an interruption of progression of the disease.

All these data indicate a probable *Borrelia burgdorferi* sensu lato infection. One could argue that the presence of IgM is significant for an early infection, but it is well known that both IgM and IgG *Borrelia*-specific antibodies may persist for years in some patients, which makes it impossible to distinguish between past and newly acquired infections based on seropositivity alone (16). Antibodies against *Borrelia burgdorferi* sensu lato in the IgM class



Figure 1 | Clinical aspect of Parry–Romberg syndrome before treatment.



Figure 2 | Clinical aspect of Parry–Romberg Syndrome after antibiotic treatment and liposuction.

were found in another report in one of two patients with Parry–Romberg syndrome (13). There are many factors (known and unknown) that affect IgM positivity and can interfere with the test and consequently the test results. A prolonged and isolated IgM response is often detected, even years later in a subset of patients. This may certainly be due to a false-positive test. On the other hand, continual IgM production with no isotype switching to IgG was postulated in patients with active disease. In our patient, we noticed a progressive decrease in the IgM titer during follow-up after antibiotic therapy.

It is also possible that two separate disease states coexisted coincidentally in this patient, with no cause-and-effect relationship. Some authors support this hypothesis (13, 14), but it is remarkable that several reports from different parts of the world show cases of Parry–Romberg syndrome associated with Lyme disease. We cannot exclude a coincidence; however, the bacteriological and serological evidence and furthermore the interruption of the disease progression after the antibiotic therapy are difficult to ignore without claiming that this association is at least suggestive. All other cases not correlated with Lyme disease still remain to be

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Literatura:

1. Canes-Nail; Navodila za uporabo.
2. Canespor krema; Povzetek glavnih značilnosti zdravila.

Samo za strokovno javnost.



Successful removal of hyperkeratotic-lichenoid reaction to red ink tattoo with preservation of the whole tattoo using a skin grafting knife

Boštjan Mlakar¹ ✉

Abstract

With the increasing popularity of tattoo body decorations, reports of medical complications with tattoos have increased in parallel. Although tattoo reactions can resolve spontaneously, they often last for months or even years, despite the various treatment methods. In our case, we present the successful removal of hyperkeratotic-lichenoid reaction to red ink using a simple and cheap skin grafting knife. The entire tattoo was preserved with a good aesthetic result with minimal scarring.

Keywords: tattoo reactions, red ink, skin grafting knife

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Introduction

Tattooing for cosmetic purposes has been increasing in recent times. With this trend, there is also an increased risk for adverse effects. Studies have reported various reactions to the salts and other components used in tattoos. When ink allergies occur, they manifest clinically with pruritus, localized edema, an eczematous eruption with serous drainage, exfoliative dermatitis, lichenoid lesions, or verrucous papules or plaques (1). Among the most common reactions, those resulting from red pigment are more frequent than from other colors (2). These may be associated with allergic contact dermatitis, lichenoid dermatitis, and pseudolymphoma (3). Treatment of cutaneous allergic reactions to tattoo ink depends on the severity of the signs and symptoms. Conservative treatment options include topical, oral, and/or intralesional steroids, oral anti-histamines, and protection from UV light. Destruction methods include cryotherapy, electrosurgery, surgical excision, dermabrasion, chemical destruction via acid, or ablation via non-Q-switched laser such as a carbon dioxide device (1). Substantial flattening and depigmentation of the red ink in the tattoos were also reported after six treatments using a Q-switched 532 nm Nd:YAG laser (4).

This case report presents a hyperkeratotic-lichenoid reaction to a red ink tattoo and successful surgical treatment with preservation of the tattoo.

Case report

A 38-year-old female patient complained of itching, followed by the appearance of raised scaly erythematous and hyperkeratotic-lichenoid lesions over the site of red ink on her lower leg. The black ink in the tattoo was not affected (Fig. 1). The tattoo had been placed 8 weeks prior to her presentation and the first symptoms occurred 3 weeks after the injection. The patient refused the suggested biopsies. Intralesional corticosteroids were administered twice in the period of 2 months and oral antihistamines were prescribed for this period. Only mild improvement of itching was achieved. The patient was referred to a laser specialist, who suggested continuous steroid therapy. We suggested experimental partial removal of the tattoo using a skin grafting knife. After another unsuccessful steroid therapy, the patient agreed with

our proposal. Eight months after the tattoo was injected, only elevated regions of red pigment were removed, using a skin grafting knife in the same manner as thin layers of burned tissue are removed (Fig. 2). We decided on that procedure because the non-surgical therapy we could offer failed and the patient demanded a quick and inexpensive solution to the problem. She agreed with complete surgical excision of the tattoo if the proposed procedure using a skin grafting knife failed or if the aesthetic result after healing the wound was not acceptable. The procedure was performed using local tumescent anesthesia. Antibiotic petroleum jelly mesh was administered and changed daily for 14 days. Once the skin had reepithelialized, topical silicon jelly was used for 2 months. The 12-month follow-up shows a good aesthetic result with minimal scarring and without any symptoms of allergy. The entire tattoo was preserved (Fig. 3).

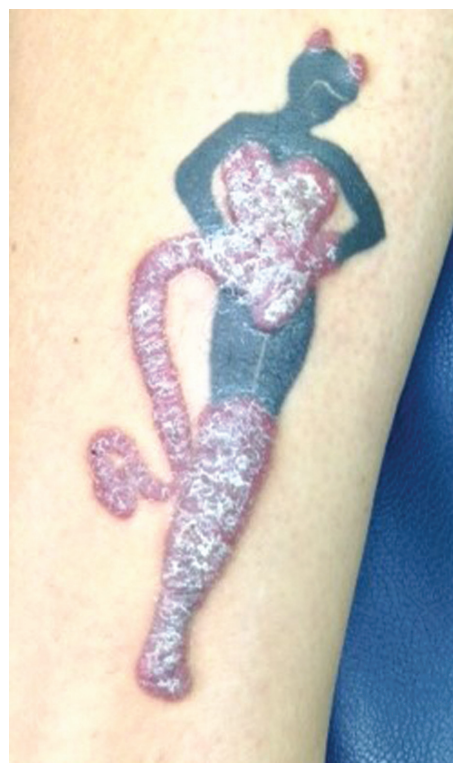


Figure 1 | Tattoo reaction before skin surgery.

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Figure 2 | Tattoo just after skin grafting procedure.

Discussion

Steroids, laser therapy, and excision are the mainstay of treatment of allergic reactions to tattoos (5). However, removal generally requires multiple forms of treatment, most of which fail to remove the colors completely, and the cosmetic results are sometimes poor after treatment, or symptoms still persist. There have been reports of local and/or widespread allergic reactions as a result of using laser to remove a normal tattoo (6, 7). During laser treatment, the tattoo pigment is released from cells into extracellular space and may be released into the vascular supply and thus recognized as foreign by the immune system, causing a hypersensi-



Figure 3 | Tattoo 12 months after skin grafting procedure.

tivity response. Anaphylactic shock is thus also a rare possibility (1). We could not find data on whether the risk of a general allergic reaction is greater in cases in which some cutaneous allergic reactions to tattoo ink already exist. Despite that risk, laser removal seems to be the second treatment method if therapy with local corticosteroids fails. Skin grafting or other abrasive procedures are usually the last option because of the non-optimal cosmetic result with more or less scarring wounds. However, in our case we were successful in removing the hyperkeratotic-lichenoid reaction to red ink using a simple and cheap skin grafting knife. We could not find any similar case in the literature involving preserving the entire tattoo using the skin grafting knife technique.

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ENBREL 50 mg raztopina za injiciranje v napolnjenem injekcijskem peresniku⁽⁴⁾

Sestava in oblika zdravila: (1) Ena viala vsebuje 25 mg etanercepta. (2) Ena napolnjena injekcijska brizga vsebuje 50 mg etanercepta. (3) Ena viala vsebuje 10 mg etanercepta. (4) En napolnjen injekcijski peresnik vsebuje 50 mg etanercepta. Etanercept je pridobljen z rekombinantno DNA tehnologijo v ovarijskih celicah kitajskega hrčka. **Indikacije:** (1, 2, 4) Revmatoidni artritis (RA) - zmeren do hud aktivni RA pri odraslih (v kombinaciji z metotreksatom), kadar odziv na zdravljenje z imunomodulatornimi zdravili, vključno z metotreksatom (če ta ni kontraindiciran), ni zadosten. Monoterapija, kadar bolnik ne prenese metotreksata ali kadar trajno zdravljenje z njim ni primerno. Hud, aktiven in napredujoč RA pri odraslih, ki se niso dobivali metotreksata. (1, 2, 3, 4) Juvenilni idiopatski artritis (JIA) - poliartritis (pozitiven ali negativen za revmatoidni faktor) in razširjen oligoartritis pri otrocih in mladostnikih, starih 2 leti ali več, ki so se nezadostno odzvali na zdravljenje z metotreksatom ali ga niso prenašali. Psoriatični artritis pri mladostnikih, starih 12 let ali več, ki so se nezadostno odzvali na zdravljenje z metotreksatom ali ga niso prenašali. Artritis, povezan z entezitisom, pri mladostnikih, starih 12 let ali več, ki so se nezadostno odzvali na konvencionalno zdravljenje ali ga niso prenašali. (1, 2, 4) Psoriatični artritis (PA) - aktiven in progresiven PA pri odraslih, če je bil odziv na zdravljenje z imunomodulatornimi zdravili nezadosten. (1, 2, 4) Ankilozirajoči spondilitis (AS) - hud aktivni AS pri odraslih, če je bil odziv na konvencionalno zdravljenje nezadosten. (1, 2, 4) Radiografsko nezaznavni aksialni spondilartritis - Zdravljenje odraslih s hudim radiografsko nezaznavnim aksialnim spondilartritisom in objektivnimi znaki vnetja, ki imajo nezadostni odziv na NSAID. (1, 2, 4) Psoriza v plaki (PP) - zmeren do hud PP pri odraslih, ki se ne odzovejo na drugo sistemsko zdravljenje, vključno s ciklosporinom, metotreksatom ali psoralenom in ultravijolično svetlobo UV-A (PUVA), oziroma je pri njih le-to kontraindicirano ali ga ne prenašajo. (1, 2, 3, 4) Otroška PP - huda kronična PP pri otrocih in mladostnikih od 6. leta starosti naprej, pri katerih se z drugo sistemsko terapijo ali fototerapijo bolezní ne da zadostno obvladati ali jih bolniki ne prenašajo. **Odmernanje in način uporabe:** Zdravljenje z Enbrelom lahko uvede in nadzoruje le zdravnik specialista, ki ima izkušnje z zdravljenjem navedenih stanj. Bolniki, ki se zdravijo z Enbrelom, naj prejmejo opozorilno kartico za bolnika. Odrasli (vse indikacije): 25 mg dvakrat na teden ali 50 mg enkrat na teden. Klinični odziv pri RA, PA, AS in radiografsko nezaznavnem aksialnem spondilartritisu je običajno dosežen v 12 tednih zdravljenja. Če v tem obdobju ni odziva, je treba o nadaljevanju zdravljenja skrbno razmisliti. PP: Če je treba je mogoče uporabljati tudi 50 mg dvakrat na teden do 12 tednov, čemur sledi 25 mg dvakrat na teden ali 50 mg enkrat na teden. Zdravljenje je treba nadaljevati do remisije, vendar največ 24 tednov. Za nekatere bolnike bo morda primerno stalno zdravljenje, daljše od 24 tednov. Če po 12 tednih ni odziva, je treba zdravljenje prekiniti. Če je indicirano ponovno zdravljenje, je odmerek 25 mg dvakrat na teden ali 50 mg enkrat na teden. **Pediatrična populacija:** JIA: Priporočeni odmerek je 0,4 mg/kg telesne mase (do največ 25 mg na odmerek) 2-krat na teden subkutano z razmikom med odmerki 3-4 dni ali 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden. **Otroška PP:** 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden do največ 24 tednov. Če je indicirano ponovno zdravljenje, je odmerek 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden. **Prekinitev zdravljenja:** o prekinitvi je treba razmisliti, če ni odziva po 4 mesecih (JIA) ali 12 tednih (otroška PP) zdravljenja. Način uporabe: subkutana injekcija. **Kontraindikacije:** Preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov, sepsa ali možnost nastanka sepse ter aktivne okužbe, vključno s kroničnimi ali lokaliziranimi okužbami. **Posebna opozorila in previdnostni ukrepi:** Okužbe: Pred zdravljenjem, med njim in po njem je treba bolnike pregledati glede okužb in pri tem upoštevati, da je povprečni razpolovni čas izločanja etanercepta iz telesa približno 70 ur (razpol 7-300 ur). Poročali so o primerih resnih okužb. Bolnike, pri katerih se med zdravljenjem pojavi nova okužba, je treba skrbno spremljati. Zdravljenje je treba prekiniti, če pride do resne okužbe. Previdnost je potrebna pri zdravljenju bolnikov s ponavljajočimi se ali kroničnimi okužbami v anamnezi ali z drugimi osnovnimi stanji, ki bi lahko povečala dovzetnost za okužbe. Tuberkuloza: Pred začetkom zdravljenja je treba vse bolnike pregledati glede aktivne kot tudi neaktivne ('latentne') tuberkuloze. Priporočljivo je, da se ti testi vpišejo v bolnikovo opozorilno kartico. Obstaja nevarnost lažno negativnih rezultatov tuberkulinskega kožnega testa, še posebej pri bolnikih, ki so hudobolni ali imunokompromitirani. Pri aktivni tuberkulozi se zdravljenje ne sme uvesti, pri neaktivni ('latentni') tuberkulozi pa je treba pred uvedbo zdravljenja in v skladu z nacionalnimi priporočili začeti zdravljenje latentne tuberkuloze s tuberkulozistiki. Vsem bolnikom je treba naročiti, naj počkejo zdravilsko pomoč, če se med zdravljenjem ali po njem pojavijo znaki/simptomi tuberkuloze. Reaktivacija hepatitisa B: Pri bolnikih, ki so kdaj že bili okuženi s HBV in so se zdravili z antagonisti TNF, vključno z Enbrelom, so poročali o reaktivaciji hepatitisa B. Pred uvedbo zdravljenja je treba bolnike preiskati na okužbo s HBV. Če je bolnik pozitiven na HBV, je pred uvedbo zdravljenja priporočljivo posvetovanje s specialistom za zdravljenje hepatitisa B. Pri dajanju Enbrela bolnikom, ki so že bili okuženi s HBV, je potrebna previdnost. Take bolnike je treba ves čas zdravljenja in še več tednov po prekinitvi spremljati glede znakov in simptomov aktivne okužbe s HBV. Če se razvije okužba s HBV, je treba zdravljenje prekiniti in uvesti učinkovito protivirusno ter ustrezno podporno zdravljenje. Hepatitis C: Poročali so o poslabšanju hepatitisa C, potrebna je previdnost. Alergijske reakcije: poročali so o alergijskih reakcijah, vključno z angioedemom in urtikarijo, opisani pa so tudi primeri resnih reakcij. Če se pojavi kakršnakoli resna alergijska ali anafilaktična reakcija, je treba zdravljenje prekiniti in uvesti ustrezno zdravljenje. (2, 4) Pokrovec igle vsebuje lateks, ki lahko povzroči preobčutljivostne reakcije, če z Enbrelom ravna oseba z znano ali možno preobčutljivostjo na lateks ali če ga damo takšni osebi. Imunosupresija: Za antagoniste TNF, vključno z Enbrelom, velja, da lahko vplivajo na naravno odpornost bolnika proti okužbam in malignim obolenjem. Bolniki, ki so poročali o uporabi antagonistov TNF pri bolnikih z anamnezo malignosti ali pri razmisleku o nadaljevanju zdravljenja pri bolnikih, pri katerih se pojavi malignost. **Kožni rak:** Pri bolnikih, zdravljenih z antagonisti TNF, vključno z Enbrelom, so poročali o melanomu in nemelanomskem kožnem raku. Priporočamo občasen pregled kože. Cepjenja: Med zdravljenjem bolnik ne sme prejeti živih cepiv. Tvorba avtoprotiteles: Zdravljenje lahko sproži nastajanje avtoimunskih protiteles. Hematološke reakcije: Poročali so o redkih primerih pancitopenije in zelo redkih primerih aplastične anemije, tudi s smrtnim izidom. Previdnost je potrebna pri bolnikih, ki imajo krvno diskrazijo v anamnezi. Vse bolnike in starše/skrbnike je treba opozoriti, da morajo v primeru pojavnosti znakov ali simptomov, ki kažejo na krvno diskrazijo ali okužbo, med zdravljenjem takoj poiskati zdravniško pomoč. V primeru krvne diskrazije je treba zdravljenje prekiniti. Nevrološke bolezni: Pri bolnikih z demielinizirajočimi obolenji, ali pri tistih, ki imajo povečano tveganje zanje, je treba pred zdravljenjem skrbno pretehtati tveganja in koristi, vključno z nevrološko oceno. Kongestivno srčno popuščanje: Pri predpisovanju bolnikom s kongestivnim srčnim popuščanjem je potrebna previdnost. Izsledki sicer še niso dokončni, vendar podatki kažejo na morebitno tendenco k poslabšanju popuščanja pri bolnikih, zdravljenih z Enbrelom. Alkoholni hepatitis: Ne sme se uporabljati za zdravljenje alkoholnega hepatitisa. Previdnost je potrebna pri uporabi pri bolnikih, ki imajo tudi zmeren do hud alkoholni hepatitis. Weganoveja granulomatoza: Enbrela ni priporočljivo uporabljati za zdravljenje te bolezni. Hipoglikemija pri bolnikih, ki se zdravijo zaradi sladkorne bolezni: Po uvedbi zdravljenja so poročali o hipoglikemiji, zato bo morda treba zmanjšati odmerek zdravila za zdravljenje sladkorne bolezni. Staršje osebe (< 65 let): Potrebna je previdnost, posebno pozornost je treba posvetiti pojavljanju okužb. **Pediatrična populacija:** Priporočamo, da pred začetkom zdravljenja, če je le mogoče, opravite vsa cepjenja v skladu z veljavnimi smernicami. Pri bolnikih z JIA, ki so se zdravili z Enbrelom, so poročali o kronični vnetni črevesni bolezni in uveitisi. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno zdravljenje z anakinom ali z abataceptom: klinična korist teh dveh kombinacij ni dokazana, zato nista priporočljivi. Sočasno zdravljenje s sulfasalazinom: potrebna je previdnost. **Ploidnost, nosečnost in dojenje:** Ženske v rodni dobi morajo med zdravljenjem in še tri tedne po prenehanju le-tega uporabljati ustrezno metodo kontracepcije. Uporaba med nosečnostjo ni priporočljiva. Etanercept prehaja placento. Uporaba živih cepiv v prvih 16 tednih po tem, ko so matere dojenčkov prejele zadnji odmerek Enbrela, pri dojenčkih običajno ni priporočljiva. Bolnica mora med zdravljenjem prenehati dojiti ali pa prekiniti zdravljenje, pri čemer je treba upoštevati tako korist dojenja za otroka kot korist zdravljenja za mater. **Neželeni učinki:** Odrasli: **Zelo pogosti** (≥ 1/10): Okužbe (vključno z okužbami zgornjih dihal, bronhitisom, cistitisom in kožnimi okužbami), reakcije na mestu injiciranja (vključno s krvavitvijo, podplutbami, eritemom, srbenjem, bolečino in oteklino). **Pogosti** (≥ 1/100 do < 1/10): alergijske reakcije, nastanek avtoprotiteles, pruritus, zvišana telesna temperatura. **Pediatrična populacija:** Na splošno so bili neželeni učinki po vrsti in pogostosti podobni tistim pri odraslih. Vrste okužb, opaženih v kliničnih preskušanjih pri bolnikih z JIA, starih 2-18 let, so bile na splošno blage do zmerne in skladne s tistimi, ki jih pogosto vidimo pri skupinah ambulantnih pediatričnih bolnikov. Hudi neželeni učinki so bili: norice z znaki in simptomi aseptičnega meningitisa, ki je izzvenel brez posledic, vnetje slepica, gastroenteritis, depresija/osebnostne motnje, kožne razjede, ezofagitis/gastritis, streptokokni septični šok (streptokokni skupine A), sladkorna bolezen tipa 1 in okužbe mehkih tkiv ter postoperativnih ran. V kliničnih preskušanjih pri bolnikih z JIA so poročali o 4 primerih sindroma aktivacije makrofagov. Viri iz obdobja trženja so pri bolnikih z JIA poročali o kronični vnetni črevesni bolezni in uveitisi. **Način in režim izdaje:** Rp/Spec. **Imetnik dovoljenja za promet:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, Velika Britanija. **Datum zadnje revizije besedila:** 25.09.2014 Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

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3 x 0,47 g gela

Hitrost v zdravljenju aktinične keratoze

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* le za zdravljenje kože pri nehiperkeratotični, nehipertrofični aktinični keratozi pri odraslih bolnikih:
le po priporočilu dermatologa ali onkologa

Enkrat dnevno, 3 zaporedne dni

Aktinična keratoza na obrazu in lasišču pri odraslih bolnikih
Eno tubo zdravila Picato® 150 µg/g gel (ki vsebuje 70 µg ingenol mebutata) je treba enkrat dnevno nanesti na prizadeti predel in postopek ponavljati 3 zaporedne dni.

Terapevtske indikacije: Zdravilo Picato® je indicirano za zdravljenje kože pri nehiperkeratotični, nehipertrofični aktinični keratozi pri odraslih bolnikih.

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Kakovostna in količinska sestava 1 g gela vsebuje 150 mg ingenol mebutata. Vsaka tuba vsebuje 70 µg ingenol mebutata v 0,47 g gela.

Terapevtske indikacije Zdravilo Picato je indicirano za zdravljenje kože pri nehiperkeratotični, nehipertrofični aktinični keratozi pri odraslih bolnikih.

Odmerjanje in način uporabe

Odmerjanje: Aktinična keratoza na obrazu in lasišču pri odraslih bolnikih Eno tubo zdravila Picato 150 µg/g gel (ki vsebuje 70 µg ingenol mebutata) je treba enkrat dnevno nanesti na prizadeti predel in postopek ponavljati 3 zaporedne dni. **Pediatrična populacija** Zdravilo Picato ni primerno za uporabo pri pediatrični populaciji. **Starejši bolniki** Prilagoditev odmerka ni potrebna.

Način uporabe: Vsebina tube zadostja za zdravljenje površine 25 cm² (npr. 5 cm x 5 cm). Vsebino tube je treba nanesti na eno zdravljeno površino velikosti 25 cm². Tuba je namenjena samo enkratni uporabi, zato jo po uporabi zavrzite. Gel iz tube iztisnite na konico prsta, ga enakomerno porazdelite po celotni površini prizadetega mesta in počakajte 15 minut, da se posuši. Vsebino ene tube lahko uporabite za zdravljenje enega mesta v velikosti 25 cm². Samo za enkratno uporabo.

Za zdravljenje vratu: Če je več kot polovica zdravljene površine na zgornjem delu vratu, je treba uporabiti odmerjanje za obraz in lasišče. Če je več kot polovica zdravljene površine na spodnjem delu vratu, je treba uporabiti odmerjanje za trup in okončine. Bolnikom naročite, naj si po nanosu zdravila Picato nemudoma umijejo roke z milom in vodo. Če se zdravi roke, je treba umiti samo prst, s katerim se je nanesel gel. 6 ur po nanosu zdravila Picato ne umivajte mesta zdravljenja in se ga ne dotikajte. Po preteku tega časa lahko zdravljeno mesto umijete z blagim milom in vodo.

Zdravilo Picato ne nanašajte takoj po prhanju ali manj kot 2 uri pred spanjem.

Po nanosu zdravila Picato zdravljene površine ne pokrivajte z neprepustnimi povoji. Optimalne učinke zdravljenja je mogoče oceniti približno 8 tednov po zdravljenju. Če se pri kontrolnem pregledu ugotovi nepopoln učinek, je treba znova skrbno oceniti zdravljenje in razmisli o ponovni obravnavi. Klinični podatki o zdravljenju za več kot en cikel zdravljenja, ki traja 2 ali 3 zaporedne dni, niso na voljo. Klinični podatki o zdravljenju več kot enega mesta niso na voljo. Klinični podatki o zdravljenju pri imunokompromitiranih bolnikih niso na voljo, vendar ni pričakovati sistemskih tveganj, saj se ingenol mebutat ne absorbira sistemsko.

Kontraindikacije Preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov.

Posebna opozorila in previdnostni ukrepi

Izpostavljenost očem Stik z očmi je treba preprečiti. Če pride do nenamerne izpostavitve, je treba oči nemudoma izprati z velikimi količinami vode in bolnik naj čim prej poišče zdravniško pomoč. Pričakovati je, da se bodo v primeru nenamerne izpostavitve oči zdravilu Picato pojavile težave z očmi, kot so bolečina očesa, edem vek in periorbitalni edem.

Zaužitje Zdravila Picato se ne sme zaužiti. Če pride do nenamernega zaužitja, naj bolnik spije veliko vode in poišče zdravniško pomoč.

Splošno Nanašanje gela Picato se ne priporoča, dokler koža, zdravljena s predhodnimi zdravili ali kirurško, ni zaceljena. Zdravilo se ne sme nanašati na odprte rane ali dele kože s poškodovano kožno pregrado. Zdravilo Picato se ne sme uporabljati v bližini oči, na notranjem predelu nosnic, na notranjem predelu ušes ali na ustnicah.

Lokalni odzivi koži Pričakuje se, da se bodo po nanosu zdravila Picato na koži pojavili lokalni odzivi, kot so eritem, prhljaj/luščenje in nastajanje krast. Lokalizirani odzivi kože so prehodni in se običajno pojavijo v 1 dnevu od začetka zdravljenja, največjo intenzivnost pa dosežejo en teden po zaključku zdravljenja. Pri zdravljenju obraza in lasišča lokalizirani kožni odzivi običajno izvenijo v 2 tednih od začetka zdravljenja, pri zdravljenju predelov na trupu in okončinah pa v 4 tednih. Učinka zdravljenja morda ne bo mogoče ustrezno oceniti, dokler se ne pozdravijo lokalni odzivi kože.

Izpostavljenost soncu Izvedene so bile študije, ki so ocenile vpliv UV-sevanja na kožo po enkratni ali večkratni uporabi gela z ingenol mebutatom, 100 µg/g. Gel z ingenol mebutatom ni pokazal nobenega potenciala za draženje zaradi svetlobe ali za fotoalergijske učinke. Vendar pa se je treba zaradi narave bolezni izogibati čezmerni izpostavitvi sončni svetlobi (tudi porjavitvenim svetilkam in solarijem) ali izpostavitvi čim bolj zmanjšati. **Obravnava aktinične keratoze** Pri lezijah, ki so klinično atipične za aktinično keratozo ali so sumljive za malignost, je treba opraviti biopsijo, za določitev primernega zdravljenja.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij Študij medsebojnega delovanja niso izvedli. Menijo, da interakcije s sistemsko absorbiranimi zdravili niso verjetne, saj se zdravilo Picato ne absorbira sistemsko.

Plodnost, nosečnost in dojenje

Nosečnost Podatkov o uporabi ingenol mebutata pri nosečnicah ni. Študije na živalih so pokazale blago toksičnost za zarodek/plod (glejte poglavje 5.3). Tveganja za ljudi, ki prejemajo kožno zdravljenje z ingenol mebutatom, so malo verjetna, saj se zdravilo Picato ne absorbira sistemsko. Iz previdnostnih razlogov se je uporabi zdravila Picato med nosečnostjo bolje izogibati.

Dojenje Učinkov na dojene novorojence/otroke se ne pričakuje, ker se zdravilo Picato ne absorbira sistemsko. Doječim materam je treba dati navodilo, da novorojenček/dojenček še 6 ur po nanosu zdravila Picato ne sme piti v tesni stik z zdravilnim mestom.

Plodnost Študij plodnosti z ingenol mebutatom niso izvedli.

Neželeni učinki

Povzetek varnostnega profila Neželeni učinki, o katerih so najpogostejše poročali, so lokalni kožni odzivi, vključno z eritemom, prhljajem/luščenjem, krastami, otekanjem, vezikulacij/pustulacij in erozijo/ulceracijo na mestu uporabe gela z ingenol mebutatom; glejte preglednico 1 za izrazo po MedDRA. Po nanosu gela z ingenol mebutatom se je pri večini bolnikov (> 95 %) pojavil en ali več lokalnih kožnih odzivov. Pri zdravljenju obraza in lasišča so poročali o okužbi na mestu nanosa.

Sesnam neželenih učinkov v obliki preglednice V preglednici 1 je prikazana izpostavitve 499 bolnikov z aktinično keratozo zdravilu Picato 150 µg/g ali 500 µg/g v štirih z vzhikom nadzorovanih študijah 3. faze, v katere sta bila skupaj vključena 1002 bolnika. Bolniki so enkrat dnevno prejemali lokalno zdravljenje (površine 25 cm²) z zdravilom Picato v koncentraciji 150 µg/g 3 zaporedne dni ali 500 µg/g 2 zaporedna dneva ali lokalno zdravljenje z vzhikom. V preglednici so predstavljeni neželeni učinki v skladu z MedDRA, razvrščeni po organskih sistemih in anatomskega mesta.

Pogostost neželenih učinkov je opredeljena kot:

zelo pogosti (≥ 1/10); pogosti (≥ 1/100 do < 1/10); občasni (≥ 1/1.000 do < 1/100); redki (≥ 1/10.000 do < 1/1.000); zelo redki (< 1/10.000) in neznan (ni mogoče oceniti iz razpoložljivih podatkov).

V razvrstitvah pogostosti so neželeni učinki navedeni po padajoči resnosti.

Opis izbranih neželenih učinkov Lokalni kožni odzivi pri zdravljenju »obraza/lasišča« oziroma »trupa/okončin«, pri katerih je bila incidenca > 1-odstotna, so: eritem na mestu uporabe (94 % oz. 92 %), luščenje kože na mestu uporabe (85 % oz. 90 %), krasta na mestu uporabe (80 % oz. 74 %), oteklina na mestu uporabe (79 % oz. 64 %), vezikule na mestu uporabe (13 % oz. 20 %), pustule na mestu uporabe (43 % oz. 23 %) in erozija mesta uporabe (31 % oz. 25 %).

Incidenca hudih lokalnih odzivov na koži obraza in lasišča je bila 29-odstotna, na koži trupa in okončin pa 17-odstotna. Hudi lokalni odzivi na koži pri zdravljenju »obraza/lasišča« oziroma »trupa/okončin«, pri katerih je bila incidenca > 1-odstotna, so: eritem na mestu uporabe (24 % oz. 15 %), luščenje kože na mestu uporabe (9 % oz. 8 %), krasta na mestu uporabe (6 % oz. 4 %), oteklina mesta uporabe (5 % oz. 3 %) in pustule na mestu uporabe (5 % oz. 1 %).

Dolgotrajno sledenje Spremljali so celokupno 198 bolnikov s popolno ozdravitvijo lezij na 57. dan (184 se jih je zdravilo z zdravilom Picato in 14 z vzhikom) še 12 mesecev. Rezultati niso spremenili varnostnega profila zdravila Picato.

Preveliko odmerjanje Preveliko odmerjanje zdravila Picato lahko povzroči povečano incidenco lokalnih odzivov kože. Obravnava prevelikega odmerjanja naj obsega zdravljenje kliničnih simptomov.

Posebna navodila za shranjevanje Shranjuje v hladilniku (2 °C - 8 °C). Odprite tube po prvem odprtju zavrzite.

Vrsta ovojnice in vsebina Vseplastne eno odmerne tube z notranjo plastjo iz polietilena velike gostote (HDPE) in aluminijasto pregrado membrano. Pokrovčki iz HDPE.

Zdravilo Picato 150 µg/g gel je pakirano v škatli s 3 tubami, od katerih vsaka vsebuje 0,47 g gela.

Imetnik dovoljenja za promet LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Danska

Datum zadnje revizije 15. 11. 2012

Zastopnik v Sloveniji Pharmagan, d.o.o., Vodopivčeva 9, 4000 Kranj

Preglednica 1 Neželeni učinki po organskih sistemih v skladu z MedDRA

Pogostost	Obraz in lasišče	Trup in okončine
Organski sistem		
Infekcijske in parazitske bolezni		
pustule na mestu nanosa	zelo pogosti	zelo pogosti
okužba na mestu nanosa	pogosti	
Bolezni živčevja		
glavobol	pogosti	
Očesne bolezni*		
edem veke	pogosti	
bolečina v očesu	občasni	
periorbitalni edem	pogosti	
Splošne težave in spremembe na mestu aplikacije		
erozija na mestu nanosa	zelo pogosti	zelo pogosti
vezikule na mestu nanosa	zelo pogosti	zelo pogosti
oteklina na mestu nanosa	zelo pogosti	zelo pogosti
luščenje kože na mestu nanosa	zelo pogosti	zelo pogosti
krasta na mestu nanosa	zelo pogosti	zelo pogosti
eritem na mestu nanosa	zelo pogosti	zelo pogosti
bolečina na mestu nanosa**	zelo pogosti	pogosti
pruritus na mestu nanosa	pogosti	pogosti
draženje na mestu nanosa	pogosti	pogosti
izcedek na mestu nanosa	občasni	
parastezija na mestu nanosa	občasni	občasni
razjede na mestu nanosa	občasni	občasni
občutek toplote na mestu nanosa		občasni

*: Oteklina na mestu nanosa na obrazu ali lasišču se lahko razširi na predel oči.

** Vključno s pekočim občutkom na mestu nanosa.

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Končno.

Prvo zdravilo z odobreno
indikacijo za zdravljenje
zmerne do hude oblike
Hidradenitis suppurativa

Bližina
me
osrečuje

Zaradi HS sem se
počutila nevredna
dotika

Manj abscesov in
manj bolečin

Počutim se dobro
sama s seboj

Zdravilo Humira je indicirano za zdravljenje
aktivne zmerne do hude oblike **hidradenitis
suppurativa** (acne inversa) pri odraslih
bolnikih, ki se ne odzovejo zadovoljivo na
konvencionalno HS zdravljenje.¹

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA Humira 40 mg raztopina za injiciranje v napolnjeni injekcijski brizgi. **Sestava:** Ena 0,8 ml napolnjena injekcijska brizga z enim odmerkom vsebuje 40 mg adalimumaba. Adalimumab je rekombinantno humano monoklonsko protiteleso. **Terapevtske indikacije:** *Revmatoidni artritis:* v kombinaciji z metotreksatom: zdravljenje zmernega do hudega aktivnega revmatoidnega artritisa pri odraslih bolnikih, kadar odziv na imunomodulirajoča zdravila, vključno z metotreksatom, ni zadosten; zdravljenje hudega, aktivnega in progresivnega revmatoidnega artritisa pri odraslih, ki prej še niso dobivali metotreksata. *Juvenilni idiopatski artritis:* Poliartikularni juvenilni idiopatski artritis (JIA): v kombinaciji z metotreksatom za zdravljenje aktivnega poliartikularnega JIA pri otrocih in mladostnikih od 2. leta starosti, ki se ne odzovejo ustrezno na eno ali več imunomodulirajočih antirevmatičnih zdravil. Artritis, povezan z entezitisom: za zdravljenje aktivnega artritisa, povezanega z entezitisom pri bolnikih, starih 6 let in več, ki so se neustrezno odzvali ali so intolerantni za običajno zdravljenje. *Ankilozirajoči spondilitis:* zdravljenje hudega aktivnega ankilozirajočega spondilitisa pri odraslih, ki se na konvencionalno terapijo ne odzovejo ustrezno. *Aksialni spondiloartritis brez radiografskega dokaza za AS:* zdravljenje odraslih s hudim aksialnim spondiloartritisom brez radiografskega dokaza za AS, toda z objektivnimi znaki vnetja s povišanimi CRP in/ali MRI, ki so nezadostno reagirali na ali ne prenašajo nesteroidnih protivnetnih zdravil. *Psoriatični artritis:* zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih, če odziv na predhodno zdravljenje z imunomodulirajočimi antirevmatikami ni bil ustrezen. *Psoriza:* zdravljenje zmerne do hude kronične psorize v plakih pri odraslih bolnikih, ki se ne odzovejo na druge sistemske terapije ali imajo kontraindikacije zanje. *Psoriza v plakih pri pediatričnih bolnikih:* zdravljenje hude psorize v plakih pri otrocih in mladostnikih od 4. leta starosti, ki so se neustrezno odzvali na ali niso ustrezni kandidati za topikalno zdravljenje in fototerapije. *Supurativni hidradenitis:* zdravljenje aktivnega zmernega do hudega hidradenitisa (acne inversa) pri odraslih bolnikih, ki se ne odzovejo zadovoljivo na konvencionalno zdravljenje. *Crohnova bolezen:* zdravljenje zmerne do hude, aktivne Crohnove bolezni pri odraslih bolnikih, ki se ne odzovejo na popoln in ustrezen cikel zdravljenja s kortikosteroidom in/ali imunosupresivom, ali pa takšno zdravljenje ni mogoče. *Crohnova bolezen pri pediatričnih bolnikih:* zdravljenje hude aktivne Crohnove bolezni pri pediatričnih bolnikih (od 6. leta starosti), ki se ne odzovejo zadovoljivo na konvencionalno zdravljenje, vključno s primarno prehransko terapijo, kortikosteroidom in imunomodulatorjem, ali pri tistih, ki imajo intoleranco ali kontraindikacije za tako zdravljenje. *Ulcerozni kolitis:* zdravljenje zmerno do močno aktivnega ulceroznega kolitisa pri odraslih bolnikih, ki se ne odzovejo zadostno na običajno zdravljenje ali le-to ni mogoče. **Odmerjanje in način uporabe:** *Odmerjanje:* Zdravljenje mora uvesti in nadzorovati zdravnik specialist. *Revmatoidni artritis:* odrasli bolnik: 40 mg adalimumaba vsak 2. teden v enkratnem odmerku v subkutani injekciji. *Ankilozirajoči spondilitis, aksialni spondiloartritis brez radiografskega dokaza za AS in psoriatični artritis:* 40 mg adalimumaba v enkratni subkutani injekciji vsak 2. teden. *Psoriza:* odrasli bolniki: začetni odmerek 80 mg subkutano, ki mu sledi 40 mg subkutano čez en teden in nato 40 mg subkutano vsak 2. teden. *Supurativni hidradenitis:* 160 mg 1. dan, sledi 80 mg 15. dan in nato 29. dan odmerek 40 mg vsak teden. *Crohnova bolezen:* med indukcijo pri odraslih bolnikih z zmerno do hudo, aktivno Crohnovo boleznijo 80 mg 0. teden in nato 40 mg 2. teden. Po indukcijskem zdravljenju je priporočeni odmerek 40 mg v subkutani injekciji vsak drugi teden. *Ulcerozni kolitis:* med indukcijo pri odraslih bolnikih z zmerno do močno aktivnim ulceroznim kolitisom 160 mg 0. teden in 80 mg 2. teden. Po indukcijskem zdravljenju 40 mg v subkutani injekciji vsak 2. teden. *Pediatrična populacija:* *Juvenilni idiopatski artritis: Poliartikularni JIA od 2. do 12. leta starosti:* 24 mg/m² telesne površine do največjega enkratnega odmerka 20 mg (za bolnike, stare 2 do < 4 leta) in do največjega enkratnega odmerka 40 mg (za bolnike, stare 4 - 12 let) adalimumaba, vsak 2. teden v subkutani injekciji; *Poliartikularni JIA od 13. leta starosti:* 40 mg adalimumaba vsak 2. teden ne glede na telesno površino. Uporaba zdravila Humira pri bolnikih, starih manj kot 2 leti, za to indikacijo ni primerna. *Pediatrični bolniki s psorizo ali ulceroznim kolitisom:* Varnost in učinkovitost zdravila Humira pri otrocih, starih 4-17 let, ni bila potrjena. Uporaba pri otrocih, starih manj kot 4 leta, za to indikacijo ni primerna. *Artritis, povezan z entezitisom:* Priporočeni odmerek pri bolnikih, starih 6 let in več, je 24 mg/m² telesne površine do največjega posamičnega odmerka 40 mg adalimumaba vsak drugi teden v subkutani injekciji. *Psoriza v plakih pri pediatričnih bolnikih:* Priporočeni odmerek je 0,8 mg na kilogram telesne mase (do največ 40 mg na odmerek), ki se ga da subkutano enkrat na teden, v primeru prvih dveh odmerkov, nato pa vsak drugi teden. *Supurativni hidradenitis pri pediatričnih bolnikih:* Varnost in učinkovitost zdravila Humira pri otrocih, starih 12-17 let, ni bila potrjena. Uporaba pri otrocih, starih manj kot 12 let, za to indikacijo ni primerna. *Pediatrični bolniki s Crohnovo boleznijo:* < 40 kg: 40 mg 0. teden, ki mu sledi 20 mg 2. teden. Po uvodnem zdravljenju je priporočeni odmerek 20 mg vsak drugi teden v obliki subkutane injekcije; ≥ 40 kg: 80 mg 0. teden, ki mu sledi 40 mg 2. teden. Po uvodnem zdravljenju je priporočeni odmerek 40 mg vsak drugi teden v obliki subkutane injekcije. Uporaba pri otrocih, starih manj kot 6 let, za to indikacijo ni primerna. *Pediatrični bolniki s psoriatičnim artritisom in aksialnim spondiloartritisom, vključno z anksiloznim spondilitisom:* Uporaba pri teh bolnikih ni primerna. **Način uporabe:** uporablja se kot subkutana injekcija. **Kontra-indikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Aktivna tuberkuloza ali druge hude okužbe in oportunistične okužbe. Zmerno do hudo srčno popuščanje. **Posebna opozorila in previdnostni ukrepi:** *Okužbe:* Bolniki so bolj dovzetni za resne okužbe. Okvarjena pljučna funkcija lahko zveča tveganje za razvoj okužbe. Bolnike je zato treba pred, med in po zdravljenju natančno kontrolirati glede okužb, vključno s tuberkulozo. *Reaktivacija hepatitisa B:* Reaktivacijo hepatitisa B so opazili pri bolnikih, ki so dobivali antagonist TNF in ki so bili kronični nosilci virusa. *Nevrološki zapleti:* Antagonisti TNF so bili v redkih primerih povezani s pojavom ali poslabšanjem kliničnih simptomov in/ali rentgenoloških znakov demielinizirajoče bolezni osrednjega živčnega sistema, vključno z multiplo sklerozo in optičnim nevritsom, in periferne demielinizirajoče bolezni, vključno z Guillain-Barré-jevim sindromom. *Malignomi in limfoproliferativne bolezni:* V kontroliranih delih kliničnih preizkušanj z antagonisti TNF je bilo opaženih več primerov malignomov, vključno z limfomi. *Hematološke reakcije:* Redko opisana pancitopenija, vključno z aplastično anemijo. *Cepfljenja:* Uporaba živih cepiv pri dojenčkih, ki so bili izpostavljeni adalimumabu in utero, ni priporočljiva še 5 mesecev po materini zadnji injekciji adalimumaba med nosečnostjo. *Kongestivno srčno popuščanje:* Pri bolnikih z blagim srčnim popuščanjem potrebna previdnost. *Avtoimunska dogajanja:* Zdravljenje lahko povzroči nastanek avtoimunskih protiteles. *Sočasna uporaba bioloških DMARDS ali antagonistov TNF:* Sočasna uporaba z drugimi biološkimi DMARDS (t.j. anakinra in abacept) ali z drugimi antagonisti TNF ni priporočljiva. *Operacije:* Bolnika, ki med zdravljenjem potrebuje operacijo, je treba natančno nadzirati glede okužb. Starejši ljudje: Posebna pozornost glede tveganja okužb. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** V kombinaciji z metotreksatom, je bilo nastajanje protiteles v primerjavi z monoterapijo manjše. Kombinacija zdravila Humira in anakinre ter zdravila Humira in abatacepta ni priporočljiva. **Nosečnost in dojenje:** Ženske ne smejo dobiti vsaj pet mesecev po zadnjem zdravljenju z zdravilom Humira. **Neželeni učinki:** *Najpogostejši neželeni učinki* so okužbe (kot je nazofaringitis, okužba zgornjih dihal in sinusitis), reakcije na mestu injiciranja (eritem, srbenje, hemoragija, bolečina ali otekanje), glavobol in mišično-skeletne bolečine. *Drugi pogostejši neželeni učinki:* različne vrste okužb; benigni tumor, karcinom kože; levkopenija, trombocitopenija, levkocitoza; preobčutljivost, alergije; zvišanje lipidov, hipokalemija, hiperurikemija, nenormalni nivo natrija v krvi, hipokalcemija, hiperglikemija, hipofosfotemija, dehidracija; spremembe razpoloženja, anksioznost, nespečnost; glavobol, parestezije, migrena, stisnjenost živčnih korenin; motnje vidnega zaznavanja, konjunktivitis, vnetje veke, otekanje oči; vertigo; tahikardija; hipertenzija, zardevanje, hematomi; kašelj, astma, dispneja; bolečine v trebuhu, navzeja in bruhanje, gastrointestinalna krvavitev, dispepsija, bolezen gastroezofagealnega refluksa, Sjögrenov sindrom; zvišani jetrni encimi; izpuščaj, poslabšanje ali pojav psorize, urtikarija, modrice, dermatitis, oniholiza, čezmerno znojenje, alopecija, srbenje; mišičnoskeletne bolečine, mišični spazmi; hematurija, ledvična okvara; reakcija na mestu injiciranja, bolečina v prsih, edemi, povišana telesna temperatura; koagulacija in motnje krvavenja, prisotnost avtoproteles, zvišanje laktat dehidrogenaze v krvi; slabše celjenje. **Način in režim izdajanja:** Predpisovanje in izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** AbbVie Ltd, Maidenhead, SL6 4UB Velika Britanija. **Datum revizije besedila:** 28.7.2015.

Vir: 1. Humira Povzetek glavnih značilnosti zdravila, julij 2015

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AbbVie Biofarmaceutvska družba d.o.o., Dolenjska cesta 242c, Ljubljana, Tel.: 01 320 80 60, Fax.: 01 320 80 61, www.abbvie.si
Samo za strokovno javnost Datum priprave: oktober 2015 SIHUD150131

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- ulceroznega kolitisa,
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- aktivne Crohnove bolezni s fistulami,
- aktivne Crohnove bolezni pri otrocih,
- ulceroznega kolitisa pri otrocih,
- revmatoidnega artritisa,
- ankilozirajočega spondilitisa,
- psoriatičnega artritisa,
- psoriaze.

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih ali na sedežu družbe Merck Sharp & Dohme! **SESTAVA:** Ena viala vsebuje 100 mg infliksimaba. Infliksimab je himerno dovesko – misje monoklonsko protiteleso IgG1 pridobljeno v mišjih hibridoma celicah s tehnologijo rekombinantne DNK. Po rekonstituciji vsebuje en mililitr 10 mg infliksimaba. **INDIKACIJE:** (i) V kombinaciji z metotreksatom za zmanjšanje znakov in simptomov revmatoidnega artritisa ter izboljšanje funkcije sklepov pri odraslih bolnikih z aktivno boleznijo, kadar odziv na protirevmatična zdravila, ki vplivajo na imunske odzivnosti, ni zadosten; in pri odraslih bolnikih s hudo, aktivno in progresivno boleznijo, ki se niso bili zdravljeni z metotreksatom ali drugimi protirevmatičnimi zdravili. (ii) Zdravljenje zmerno do močno aktivne Crohnove bolezni pri odraslih bolnikih, ki se niso odzvali na celoten in ustrezen ciklus konvencionalnega zdravljenja. (iii) Zdravljenje hude, aktivne Crohnove bolezni pri otrocih in mladostnikih, starih od 6 do 17 let, ki se niso odzvali na običajno terapijo, ter pri tistih, ki ne prenašajo teh običajnih načinov zdravljenja oziroma imajo kontraindikacije zanje. (iv) Zdravljenje zmerno do močno aktivnega ulceroznega kolitisa pri odraslih bolnikih, ki so se nezaudostno odzvali na običajno zdravljenje, na primer na kortikosteroide in 6-MP ali AZA, ter pri tistih, ki ne prenašajo takšnega zdravljenja ali imajo medicinske kontraindikacije zanj. (v) Zdravljenje močno aktivnega ulceroznega kolitisa pri pediatricnih bolnikih, starih od 6 do 17 let, ki so se nezaudostno odzvali na običajno zdravljenje. (vi) Zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih bolnikih v primeru nezaudostnega odziva na predhodno zdravljenje s protirevmatičnimi zdravili DMARD v kombinaciji z metotreksatom ali samostojno pri bolnikih, ki ne prenašajo metotreksata ali pri katerih je metotreksat kontraindiciran. (vii) Zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih bolnikih v primeru nezaudostnega odziva na predhodno zdravljenje s protirevmatičnimi zdravili DMARD v kombinaciji z metotreksatom ali samostojno pri bolnikih, ki ne prenašajo metotreksata ali pri katerih je metotreksat kontraindiciran. (viii) Zdravljenje zmerno do hude psoriaze s plaki pri odraslih bolnikih, ki se niso odzvali na druge sistemske terapije ali pa imajo kontraindikacije zanje ali jih ne prenašajo. **ODMERJANJE IN NAČIN UPORABE:** Rumatoidni artritis: Odmerek je 3 mg/kg v intravenski infuziji v času 2 ur. Temu naj sledita dodatni infuziji z odmerkom 3 mg/kg, 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Če se bolnik nezaudostno odzove na zdravlilo ali če pri njem odziv pozneje izgine, mu lahko tudi postopoma povečujete odmerek za približno 1,5 mg/kg na vsakih 8 tednov, do največ 7,5 mg/kg. Druga možnost pa je, da bolniku daste 3 mg/kg že na vsake 4 tedne. Zmerno do močno aktivna Crohnova bolezen: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, temu pa naj sledita še dodatni infuziji zdravila v odmerku 5 mg/kg v 2. tednu po prvi infuziji. Če se bolnik ne odzove na zdravljenje po 2 odmerkih zdravila, mu ne smete več dajati infliksimaba. Pri bolnikih, ki so se odzvali na zdravlilo, so druge možnosti nadaljnjega zdravljenja naslednje: Zdravilno zdravljenje: Dodatni infuziji z odmerkom 5 mg/kg 6 tednov po prvem odmerku, temu naj sledijo infuzije na vsakih 8 tednov, ali ponovno dajanje zdravila: Infuzija odmerka 5 mg/kg, če se ponovijo znaki in simptomi bolezni. Aktivna Crohnova bolezen s fistulami: Intravenska infuzija 5 mg/kg v času 2 ur naj sledita dodatni infuziji 5 mg/kg 2 in 6 tednov po prvi infuziji. Pri bolnikih, ki se odzovejo na zdravlilo, so možnosti nadaljnjega zdravljenja naslednje: Vzdrževanje: Dodatne infuzije z odmerkom 5 mg/kg na vsakih 8 tednov, ali ponovno dajanje: Infuzija 5 mg/kg zdravila, če se ponovijo znaki in simptomi bolezni, temu naj sledijo infuzije z odmerkom 5 mg/kg na vsakih 8 tednov. Ulcerozni kolitis: Odmerek je 5 mg/kg v obliki intravenske infuzije, ki naj traja 2 uri. Temu naj sledita dva dodatna infuzijska odmerka po 5 mg/kg v 2. in 6. tednu po prvi infuziji, potem pa zdravlilo infundirajte bolniku na vsakih 8 tednov. Ankilozirajoči spondilitis: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, temu naj sledita dodatni infuziji z odmerkom 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Psoriatični artritis: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, temu naj sledita dodatni infuziji z odmerkom 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Psoriaza: 5 mg/kg, dano v obliki 2 urne intravenske infuzije, potem pa dodatne infuzije odmerkov 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Ponovna uporaba zdravila za vse indikacije: V primeru prekinitev vzdrževalnega zdravljenja, ni priporočljiva ponovna uporaba uvedne sheme. V tem primeru bolniku najprej ponovno uvedite zdravilo Remicade v enkratnem odmerku, pozneje pa mu spet predpišite vzdrževalni odmerek zdravila v skladu s priporočili, ki so podana zgoraj. Crohnova bolezen (pri bolnikih, starih od 6 do 17 let): Običajen odmerek je 5 mg/kg. Bolniku ga dajte v obliki 2 urne intravenske infuzije, ki naj ji sledita še dve infuziji v istem odmerku, in sicer 2 in 6 tednov po prvi infuziji, potem pa nadaljujte z infuzijami za vzdrževalno zdravljenje na vsakih 8 tednov. Ulcerozni kolitis (od 6 do 17 let): Odmerek je 5 mg/kg v intravenski infuziji, ki traja 2 uri. Temu naj sledita dodatni infuziji z odmerkom 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Skrajšane infuzije pri indikacijah za odrasle bolnike: Pri skrbno izbranih bolnikih, ki so dobro prenesli vsaj 2 začetne 2-urne infuzije zdravila Remicade in so trenutno na vzdrževalnem zdravljenju, lahko razmislite o skrajšanju naslednjih infuzij, vendar ne na manj kot 1 uro. Če pri skrajšani infuziji nastopi njo povečana reakcija je treba zdravljenje nadaljevati, lahko pri naslednjih infuzijah razmislite o uporabi manjše hitrosti infundiranja. Uporabe skrajšanih infuzij v odmerku > 6 mg/kg niso proučevali. **KONTRAINDIKACIJE:** Bolniki z anamnezo preobčutljivosti na infliksimab, druge misije beljakovine ali katero od pomožnih snovi. Bolniki s tuberkulozo ali z drugimi hudimi okužbami, kakor so npr. sepsa, abscesi in oportunistične okužbe. Bolniki z znemim do hudim srčnim popuščanjem (razred III/IV po NYHA). **POVZETEK POSEBNIH OPOZORIL, PREVIDNOSTNIH UKREPOV IN INTERAKCIJ:** Za izboljšanje sledljivosti bioloških zdravil, mora biti v kartoteki bolnika, ki zdravilo prejema, jasno dokumentirano (ali navedeno), zaščiteno ime in številka serije zdravila. Zdravljenje z infliksimabom je bilo povezano z akutnimi infliksimabnimi reakcijami, vključno z anafilaktičnim šokom in poznimi preobčutljivostnimi reakcijami. Če se pojavi akutna infliksimabna reakcija, morate infuzijo takoj prekiniti. Na voljo morajo biti sredstva za nujno pomoč. Za preprečevanje blagih in prehodnih učinkov lahko bolnikom pred zdravljenjem z zdravilom Remicade daste premedikacijo. Če se pojavijo resne reakcije, morate uvedi simptomatično zdravljenje in bolniku ne smete več dajati infuzij tega zdravila. Če bolnik po daljšem obdobju ponovno prejme zdravilo Remicade, ga morate skrbno spremljati zaradi morebitnega pojava znakov in simptomov pozne preobčutljivosti. Pred, med in po zdravljenju z zdravilom Remicade morate bolnike skrbno spremljati, da ugotovite morebitne okužbe, npr. tuberkulozo. Bolnika ne smete več zdraviti s tem zdravilom, če dobi resno okužbo ali sepsa. Zaviranje TNF- α lahko prikrije simptome okužbe. Bolniki, ki jemljejo zaviralce TNF, so bolj občutljivi za resne okužbe. Uporabo zdravila Remicade prekinite, če se pri bolniku pojavi nova resna okužba ali sepsa, in mu uvedite ustrezno protimikrobno ali protiglivično terapijo, dokler ne bo okužba obvladana. Pred začetkom zdravljenja z zdravilom Remicade, morate vse bolnike pregledati in preiskati, da ugotovite morebitno aktivno ali neaktivno tuberkulozo. Če se pri bolnikih, zdravljenih z zdravilom Remicade, razvije resna sistemska bolezen, je treba posumiti na invazivno glivično okužbo, kot so aspergiloza, kandidiaza, pneumocistoza, histoplasmoza, kokcidiodiomioza ali blastomikoza, poleg tega pa je pri teh bolnikih že zgodaj v poteku preiskav potreben posvet z zdravnikom, ki ima strokovno znanje iz diagnostike in zdravljenja invazivnih glivičnih okužb. Bolnike, pri katerih obstaja tveganje za okužbo z virusom hepatitisa B, je treba oceniti, ali imajo znake okužbe s HBV, preden smete pri njih uvedi zdravljenje z zdravilom Remicade. Bolnike s simptomi ali znaki motenj delovanja jeter morate pregledati oz. opraviti preiskave, da ugotovite morebitne znake poškodbe jeter. Kombiniranje zdravila Remicade in abatacepta oz. anakinere ni priporočljivo. Priporočamo, da živih cepiv in povzročiteljev okužb v terapevtske namene ne dajete sočasno z zdravilom Remicade. Pri pediatricnih bolnikih s Crohnovo boleznijo če je le mogoče opravite vsa cepljenja, v skladu s tekočimi veljavnimi smernicami za cepljenje otrok, preden pri njih uvedete zdravljenje z zdravilom Remicade. Relativno pomanjkanje TNF- α kot posledica anti TNF terapije lahko sproži avtoimunski proces. Infliksimab in druga zdravila, ki zavirajo TNF- α , so bila v redkih primerih povezana z nevritisom vidnega živca, epileptičnimi napadi in novim pojavom ali poslabšanjem kliničnih simptomov in/ali z rentgenskimi znaki demielinizirajoče bolezni osrednjega živčevja, vključno z multiple sklerozo in demielinizirajoče bolezni perifernega živčevja, vključno z Guillain-Barréjevimi sindromi. Pri odločanju o uvedbi zdravljenja pri bolnikih, ki so težko kadični in imajo zato povečano tveganje za nastanek rakave bolezni, je potrebna previdnost. Glede na sedanje znanje ni mogoče izključiti tveganja za pojav limfomov ali drugih malignih bolezni pri bolnikih, zdravljenih z zaviralci TNF. Previdnost je potrebna tudi pri odločanju o uvedbi zdravljenja z zaviralci TNF pri bolnikih z rakavimi boleznimi in pretekli anamezi ter pri odločanju o tem, ali naj nadaljujejo z zdravljenjem pri bolnikih, pri katerih se pojavi nova nova rakava bolezen. Zdravilo Remicade morate uporabljati previdno pri bolnikih z blagim srčnim popuščanjem (razred I/II po NYHA). Pri bolnikih, ki so jemali zaviralce TNF, vključno z zdravilom Remicade, so poročali o pojavu pancitopenije, levkopenije, nevropenije in trombocitopenije. Pri bolnikih, zdravljenih z zdravilom Remicade, ki so bili stari 65 let ali več, je bila incidenca resnih okužb večja kot pri bolnikih, ki so bili mlajši od 65 let. Pri zdravljenju starostnikov je torej treba posvetiti posebno pozornost tveganju za nastanek okužbe. Obstajajo znaki, da sočasna uporaba metotreksata in drugih imunomodulatorjev pri bolnikih z revmatoidnim artritisom in Crohnovo boleznijo zmanjša tvorbo protiteles proti infliksimabu in poveča koncentracijo infliksimaba v plazmi. In pri 16,5 % bolnikov iz kontrolne skupine. Med najpogostejše neželenne učinke zdravila, o katerih so poročali pri uporabi zdravila Remicade, sodijo reakcija HBV, kronično srčno popuščanje, resne okužbe (vključno s sepsa, oportunističnimi okužbami in TB), serumska bolezen (pozne preobčutljivostne reakcije), hematološke reakcije, sistemske eritematozne lupus/lupus podobne sindrom, demielinizirajoče bolezni, dogodki v zvezi z jetri ali žolčnikom, limfom, hepatosplenični limfom celic (HSTCL), črevesni ali perianalni abscesi (pri Crohnovi bolezni) ter resne z infuzijo povezane reakcije. **NAČIN IN REŽIM IZDAJE ZDRAVILA:** Zdravilo je zaradi svojih lastnosti, svoje relativne novosti ali zaradi varovanja javnega zdravja namenjeno izključno za zdravljenje, ki ga je mogoče spremljati samo v bolnišnici. **IMETNIK DOVOLJENJA ZA PROMET ZDRAVILOM:** Janssen Biologics B.V., Einsteinweg 101, 2333-CB Leiden, Nizozemska **DATUM ZADNJE REVIZIJE BESEDILA:** 25. julij 2013 **PRIPRAVLJENO V SLOVENIJO:** junij 2014. Za dodatne informacije pokličite na predstavnika Merck Sharp & Dohme, inovativna zdravila d.o.o., Smartinska cesta 140, 1000 Ljubljana, tel: 01/5204 349, faks: 01/5204 350. **LITERATURA:** Povzetek glavnih značilnosti zdravila Remicade. **IZDAL IN ZALOŽIL:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Smartinska cesta 140, 1000 Ljubljana. **SAMO ZA STROKOVNO JAVNOST.** GAST-1122414-0001 EXP: 10/2016

HITER, MOČAN IN PODALJŠAN UČINEK!

BELODERM

0,05 % betametazondipropionat

beloderm

Beloderm sedaj na voljo v 3 oblikah:

1. krema - za zdravljenje akutnih, eksudativnih kožnih sprememb
2. mazilo - za zdravljenje kroničnih dermatoz ter ko je potreben okluzivni učinek

3. **NOVO!** dermalna raztopina - za zdravljenje dermatoz na lasišču in na poraščenih delih telesa



Optimalno zdravljenje lasišča in poraščenih delov kože

Edini betametazon v obliki dermalne raztopine

Enostavno nanašanje

Ne masti kože



Uporaba zdravila Beloderm 0,5 mg/g dermalna raztopina:

- Nekaj kapljic zdravila bolnik nanese (s pomočjo kapalke) na prizadeto kožo 2 x/dan in nežno vtre
- Po nanosu se zdravila ne izpira
- Po nanosu zdravila si umije roke

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

SESTAVA: 1 gram kreme, mazila ali dermalne raztopine vsebuje 0,5 mg betametazona. **INDIKACIJE:** Bolezni kože, ki jih zdravimo z lokalnimi kortikosteroidi: **alergijske bolezni kože** - akutne, subakutne in kronične oblike kontaktnega alergijskega dermatitisa, profesionalnega dermatitisa, atopični dermatitis (nevrodermatitis), dermatitis pod plenico, intertriginozni dermatitis, ekcematozni numularni dermatitis, dishidrotični dermatitis; **akutni in kronični nealergijski dermatitisi** - fotodermatitis, dermatitis kot posledica rentgenskega sevanja, toksične reakcije zaradi pikov insektov; **druge bolezni kože** - psoriasis vulgaris, pemphigus vulgaris, lichen ruber planus, lichen simplex chronicus, lupus erythematosus chronicus discoides, erythrodermia, erythema exsudativum multiforme, erythema anulare centrifugum in druge vrste eritemov. **ODMERJANJE:** Zdravljenje naj ne bo daljše od 3 tednov. Količino zdravila Beloderm krema, mazilo ali dermalna raztopina, ki je potrebna za prekritje obsele površine kože, z rahlim vtiranjem nanašamo v tankem sloju dvakrat na dan. Na področjih kože z debelim roževinastim slojem je potrebna pogostejša aplikacija. Zdravljenje je potrebno nadaljevati do kliničnega izboljšanja. Pri uporabi zdravila Beloderm krema ali mazilo pri otrocih je potrebna previdnost, uporaba zdravila naj bo čim krajša. Varnost in učinkovitost zdravila Beloderm dermalna raztopina pri otrocih, mlajših od 18 let, še nista bili dokazani. Če zdravilo Beloderm uporabljate na obrazu ali pri otrocih, zdravljenje ne sme trajati več kot 5 dni. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožni snov, virusna okužba s kožnimi spremembami (herpes, norice, koze), kožna tuberkuloza in kožne spremembe pri lusu, akne, rozacea, perioralni dermatitis. **POSEBNA OPOZORILO IN PREVIDNOSTNI UKREPI:** Če pri prvi uporabi zdravila Beloderm nastopi preobčutljivostna reakcija na koži je treba terapijo takoj prekiniti. Uporaba zdravila Beloderm ni priporočljiva v kombinaciji z okluzivnimi povoji, razen, če tako predpiše zdravnik. Dolgotrajna uporaba na koži obraza ni priporočljiva, ker lahko povzroči dermatitis, ki se kaže kot rozacea, perioralni dermatitis in akne. Zdravilo se ne sme uporabljati na očeh ali v periokularnem območju zaradi možnosti nastanka katarakte, glavkoma, glivične okužbe oči in poslabšanja okužbe z virusom herpesa. Zdravilo Beloderm se ne sme uporabljati za zdravljenje varikoznih ulkusov goleni. Pri otrocih, zaradi večje površine kože glede na telesno maso in nezadostno razvito roženo plast kože, obstaja možnost sistemske absorpcije sorazmerno večje količine betametazona, kar lahko vodi do manifestacij sistemske toksičnosti. Izogibati se je treba uporabi pod plenici (še zlasti plastičnimi), ker le te delujejo kot okluzija in prav tako lahko povzročijo večjo absorpcijo učinkovin. Pri otrocih, bolnikih z jetrno insuficienco in bolnikih, ki potrebujejo dolgotrajno zdravljenje, je potrebna previdnost, še zlasti pri hkratni uporabi okluzivnega povoja zaradi možnosti povečane absorpcije betametazona in pojava sistemskih neželenih učinkov. Na nekaterih delih telesa, kjer obstaja neke vrste naravna okluzija (dimlje, pazduha in perianalno področje), je pri lokalni uporabi zdravila Beloderm možen nastanek strij, zato naj bo uporaba zdravila na teh delih telesa čim bolj omejena. Lahko se pojavijo simptomi, povezani z odtegotovanjem zdravila, v teh primerih je potrebno nadomestno jemanje kortikosteroidov. V primeru glivičnih ali sekundarnih bakterijskih infekcij kožnih lezij je potrebna dodatna uporaba protimikotikov oz. antibiotikov. Na lasišču je treba zdravilo Beloderm uporabljati previdno zaradi izredno močne prekrvavitve in povečane absorpcije. Zdravilo Beloderm 0,5 mg/g krema vsebuje cetil in stearylalkohol, ki lahko povzročijo lokalne kožne reakcije. **INTERAKCIJE:** Medsebojno delovanje zdravila Beloderm z drugimi zdravili ni znano. **NOSEČNOST IN DOJENJE:** Uporaba zdravila Beloderm je pri nosečnicah dovoljena samo v primeru, ko zdravnik oceni, da je pričakovana korist za mater večja od možnega tveganja za plod. V takih primerih je treba uporabljati najmanjše učinkovite odmerke čim krajši čas na čim manjši telesni površini. Po presoji zdravnika lahko zdravilo Beloderm uporabljajo tudi doječe matere, vendar se zdravilo pred dojenjem ne sme nanašati na kožo dojke. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Zdravilo Beloderm nima vpliva na sposobnost vožnje in upravljanja s stroji. **NEŽELENI UČINKI:** Pogosti: sekundarne okužbe, občutek pečenja, srbenje, draženje, suhost, folikulitis, hipertrichoza, aknam podobni izpuščaji, hipopigmentacija, teleangiektazije, perioralni dermatitis, maceracija kože, atrofija kože, strije, miliarja. **Redki:** insuficienca nadledvične žleze. **VRSTA OVOJNINE IN VSEBINA:** Škatla s tubo po 40 g kreme ali mazila; vsebnik s 100 ml dermalne raztopine (bela plastenka z rumeno varnostno navojno zaporko iz HDPE in bela kapalčka iz LDPE). **REŽIM IZDAJE:** Zdravilo se izdaja samo na recept. **IMETNIK DOVOLJENJA ZA PROMET:** Belupo d.o.o., Dvoržakova 6, 1000 Ljubljana, Slovenija. **DATUM ZADNJE REVIZIJE BESEDILA:** 11.04.2014.

Gradivo je namenjeno samo strokovni javnosti. Podrobnejše informacije o zdravilu in povzetek glavnih značilnosti zdravila so vam na voljo pri strokovnih sodelavcih in na sedežu podjetja Belupo. Datum priprave informacije: februar 2015



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