Introduction and review of new topical medicines in treatment of common skin diseases

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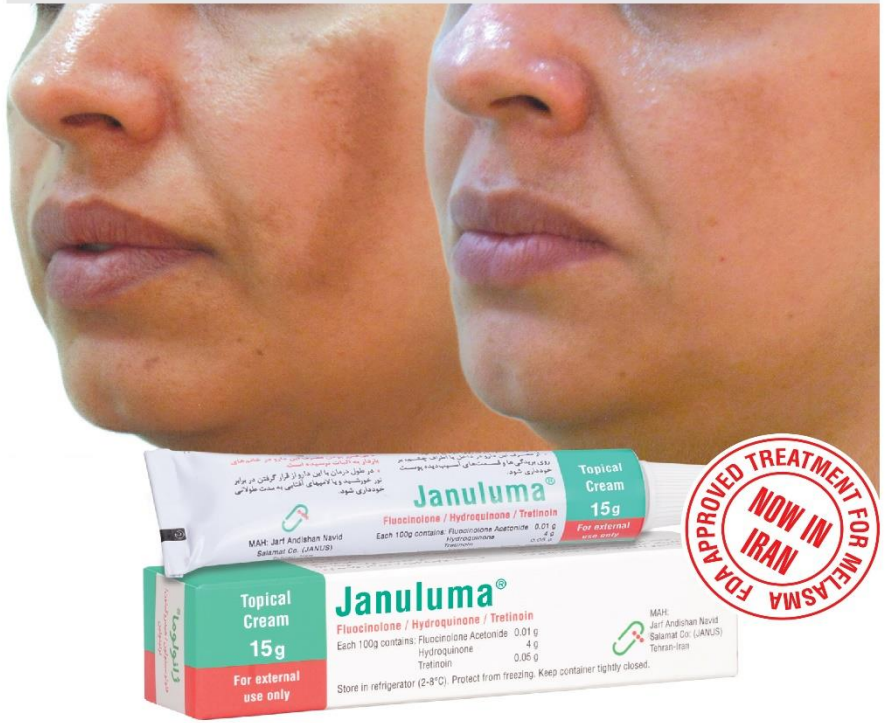
Januluma

Fluocinolone / Hydroquinone / Tretinoin

SAY GOODBYE TO DARK SPOTS



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Triple Combination

- As the gold standard in the treatment of hyperpigmentation disorders, hydroquinone is often combined with different agents including retinoids, corticosteroids, glycolic acid, kojic acid and ascorbic acid.

- For melasma, in one split-face trial, a gel containing glycolic acid, hydroquinone and kojic acid showed more improvement (60%) in patients than a gel that contained only glycolic acid and hydroquinone (47.5%).

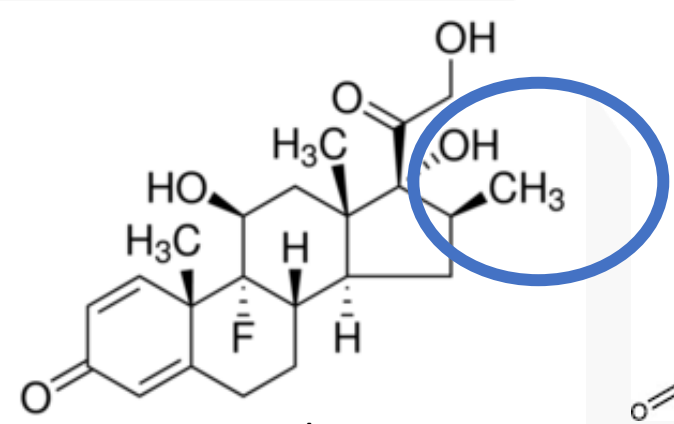
Triple Combination – Kligman Formula

- First proposed by Kligman and Willis, the original combination contained 5% hydroquinone, 0.1% tretinoin and 0.1% dexamethasone to be applied daily for 5 to 7 weeks, and it was found to be effective in the treatment of melasma.

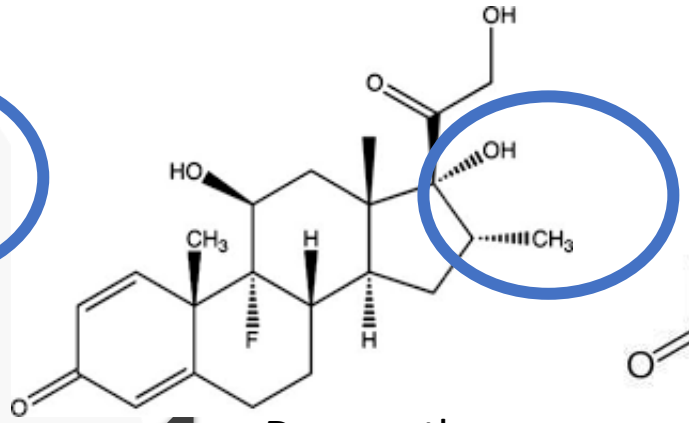
- This preparation contains high concentrations of TRE and HQ, and holds dexamethasone, which is a potent fluorinated steroid.

Triple Combination – Steroid comparison

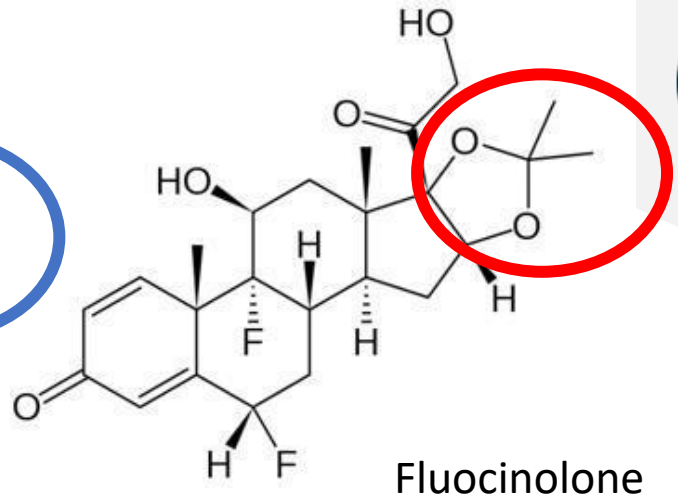
- Also, covering or removing the hydrophilic part in the position of 17 dihydroxy acetonide or 16-α-hydroxy, increases the lipophilicity of the molecule and thus increases the penetration in SC.



Betamethasone



Dexamethasone



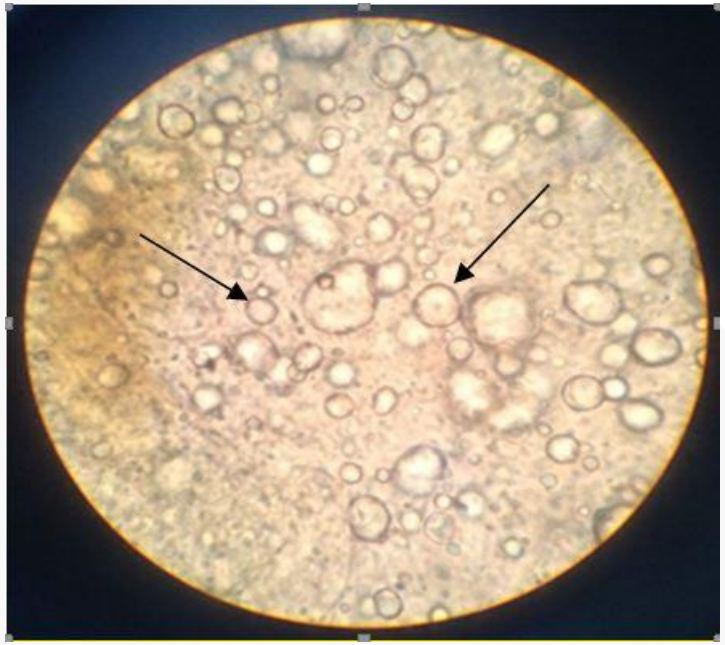
Fluocinolone

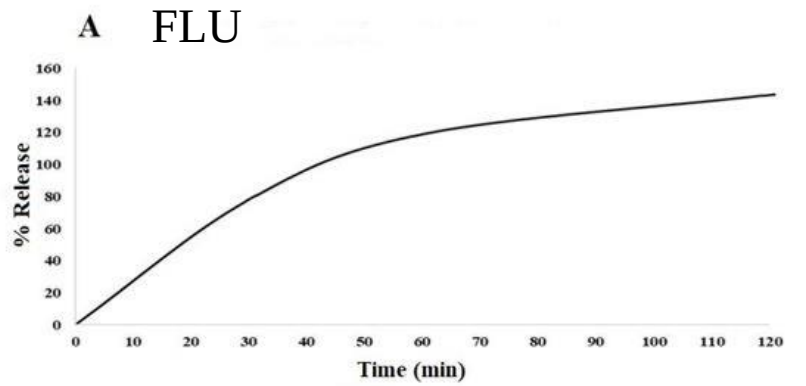
Fluocinolone acetonide (fluorine steroids)

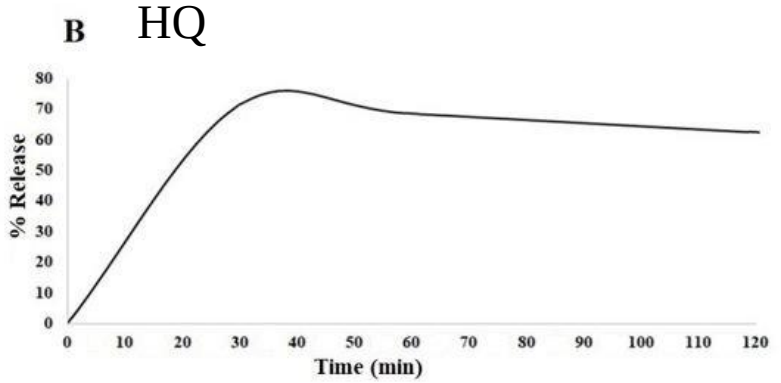
Superior steroid in treatment of hyperpigmentation

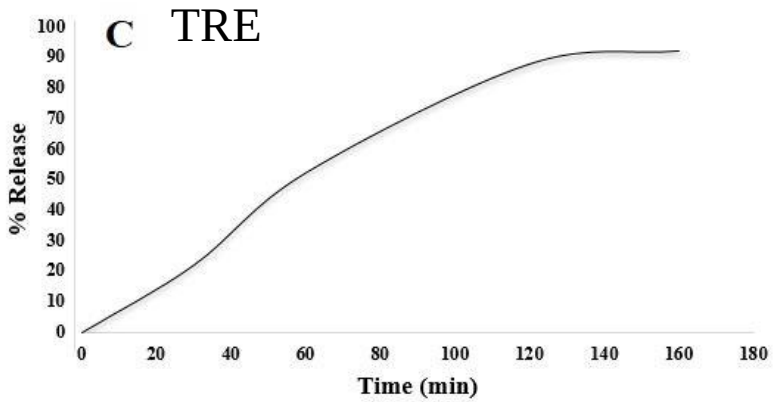
One of the most **successful combination** formulations has been **4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide**.

In a multicentre, investigator-blinded, randomized trial in patients with melasma, this triple combination cream was found to be more efficacious than dual-combination creams containing either hydroquinone plus tretinoin.









Cumulative drug release

Clinical study

Clinical Trial

Phase IIb

Single group, before after clinical study

8 weeks Follow Up

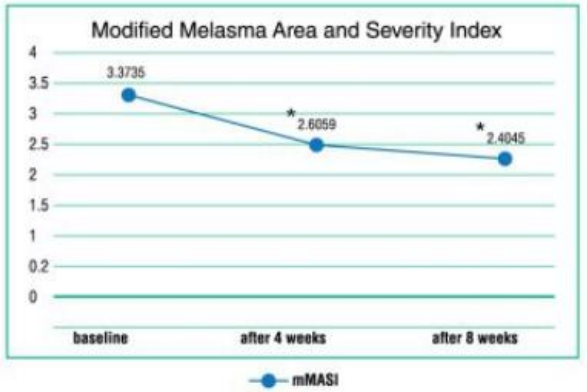
25 patients screened
22 patients enrolled
20 patients analyzed

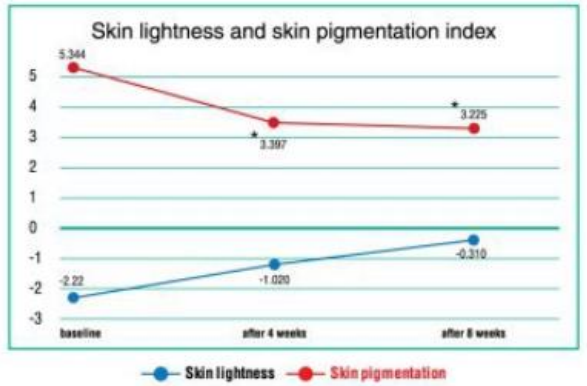
Female

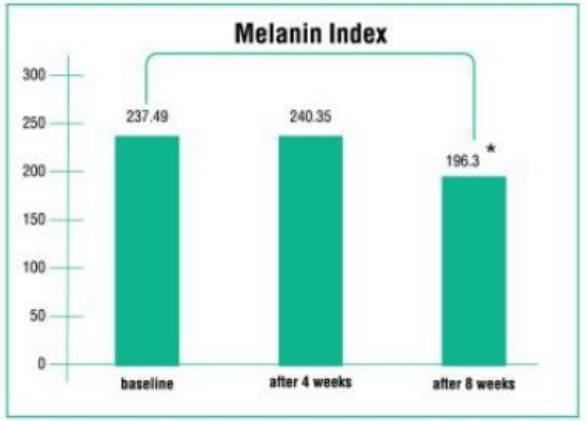
Age: 39.20 ± 4.16

Study Center
Tehran, Iran

Daily Application







*statistically significant compared to the baseline

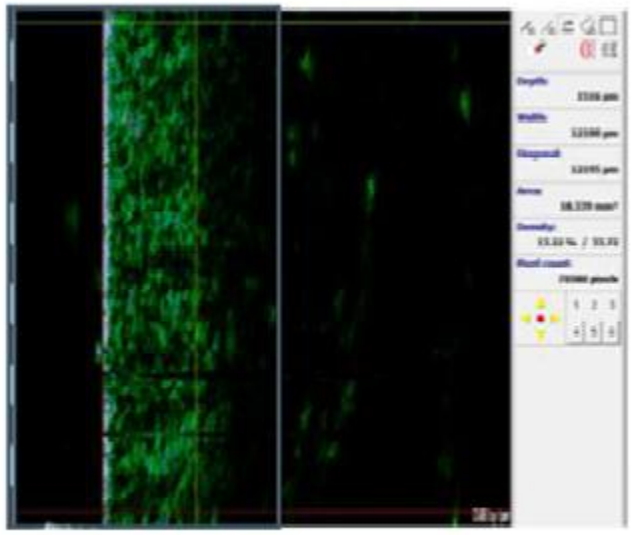
Comparison of changes in skin biophysical variables in baseline, 4 and 8 weeks after treatment

Variables	Baseline	After 4 weeks	After 8 weeks	p-value 1	p-value 2
TEWL	24.18± 13.03	30.70± 10.87	36.58± 17.01	0.087	0.000
Hydration	75.19± 16.51	76.54± 19.48	80.82± 15.50	0.770	0.317
Erythema index	385.85± 72.26	398.04±77.70	400.29± 67.20	0.352	0.292
sebum	22.42± 28.88	15.76± 12.22	8.88± 5.45	0.051	0.197
pH	6.93± 0.66	6.75± 0.67	7.03± 0.607	0.0687	0.417

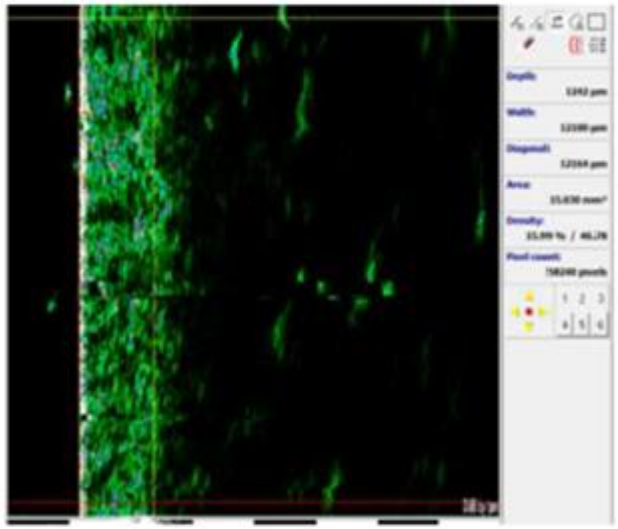
Comparison of ultra sonographic indices

Variables	Baseline	After 4 weeks	After 8 weeks	p-value 1	p-value 2
epidermis Thickness	132.99± 43.59	120.45±35.34	171.23± 240.62	0.177	0.586
Epidermal density	109± 55.13	201.96± 249.38	158.44± 163.64	0.101	0.312
Dermis thickness	1365.13± 234.30	1354.95± 261.37	1276.29± 193.74	0.889	0.524
Dermis density	27.56	31.41± 11.90	41.86± 20.25	0.329	0.029

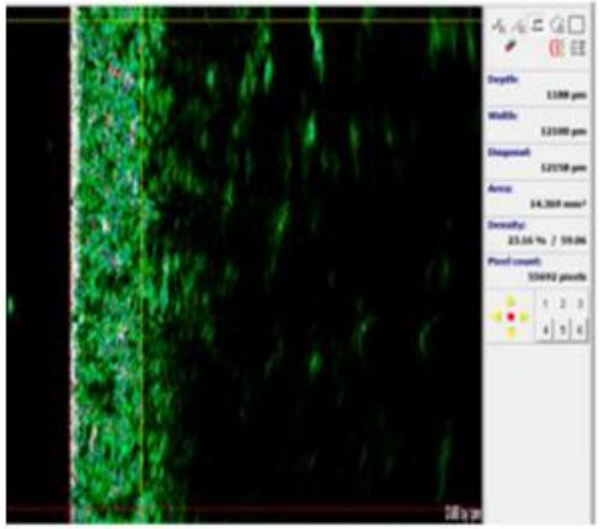
Comparison of ultra sonographic



Before



After 4 weeks



After 8 weeks

RESEARCH LETTERS

Melasma Treatment With Pulsed-Dye Laser and Triple Combination Cream: A Prospective, Randomized, Single-Blind, Split-Face Study

Recent data show that melasma lesions have, in addition to increased pigmentation, more elastosis and vascularization than perilesional skin.[1-3] The stabilized formulation of Kligman preparation has shown significant improvements in the treatment of melasma.[4] However, most of the treatments only target the pigmentation, and none of them has been demonstrated so far to prevent the frequent relapses.

Pulsed-dye laser treatment (PDL) is considered the gold standard therapy for vascular lesions. By targeting not only melanin but also vascularization and at least in part elastosis, PDL might provide, in combination with blanching cream, an effective and complete therapeutic approach for melasma. The objective of this pilot study was to evaluate the dual treatment of fixed triple combination cream (TCC) and PDL in the treatment of melasma.

Methods. We conducted a controlled, randomized, single-blind, split-face clinical trial. Patients seeking treatment for melasma were included. Exclusion criteria were skin phototype V, medical history of allergy to the compounds of the TCC, or current pregnancy or breastfeeding.

All patients applied to the entire face the TCC containing hydroquinone, 4%; tretinoin, 0.05%; and fluocinolone acetonide, 0.01% (Tri-Luma Cream; Galderma Laboratories LP, Fort Worth, Texas), once a day for 4 months. The PDL treatment (Vbeam; Candela Corporation, Wayland, Massachusetts) was started after 1 month of TCC applications. Three sessions of PDL were performed at 3-week intervals on the half face that was randomly assigned. For each session, a first passage was performed on melasma lesions aiming at removing the hyperpigmentation (compression handpiece of 10 mm; pulse duration, 1.5 milliseconds; fluency, 7 J/cm^2). A second passage was performed immediately afterwards, using a regular handpiece of 7 mm in diameter on the entire hemiface with a 10% overlap of treatment spots to target the vessels (pulse duration, 20 milliseconds; fluency, 10 J/cm^2; dynamic cooling device, 30/40). All the patients were told to apply the entire face a sunscreen of sun protection factor 50 or higher (combining Mexoryl SX and XL; L'Oreal, Paris, France) during the entire study duration.

The main criterion of evaluation was the Melasma Area and Severity Index (MASI)[5] calculated by an independent physician blinded to treatment on standardized digital photographs (VISIA; Canfield Imaging Systems, Fairfield, New Jersey). Tolerance and satisfaction were graded by the patients on a visual analog scale (VAS). To avoid confusion of results possibly caused by spontaneous improvement of melasma that is usually observed during autumn and winter months, all the patients were included at the end of winter season and a final visit was scheduled after the summer, at least 2 months after the last treatment.

Table. Comparisons of MASI Scores[a] Between Treatment Types and Evaluation Times[b]

Treatment Type	Before Treatment	End of Treatment	*P* Value[c]	Follow-up Visit After 1 Summer	*P* Value[d]
All patients (n = 17)					
TCC	6.76 (3.25)	4.35 (2.76)	.003	6.06 (3.86)	.13
TCC plus PDL	6.20 (3.02)	2.79 (2.70)	.001	4.15 (3.89)	.01

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TCC plus PDL	6.20 (3.02)	2.79 (2.70)	.001	4.15 (3.89)	.01
P value[e]	.28	.03		.02	
Phototypes II or III (n = 11)					
TCC	6.31 (2.98)	4.02 (2.62)	.03	5.46 (3.88)	.23
TCC plus PDL	5.36 (2.62)	1.72 (1.12)	.003	2.25 (2.44)	.01
P value[e]	.08	.01		.005	
Phototype IV (n = 6)					
TCC	7.65 (3.88)	4.96 (3.15)	.03	7.14 (3.93)	.35
TCC plus PDL	7.90 (3.28)	4.74 (3.69)	.046	7.64 (3.73)	.67
P value[e]	.47	.92		.53	

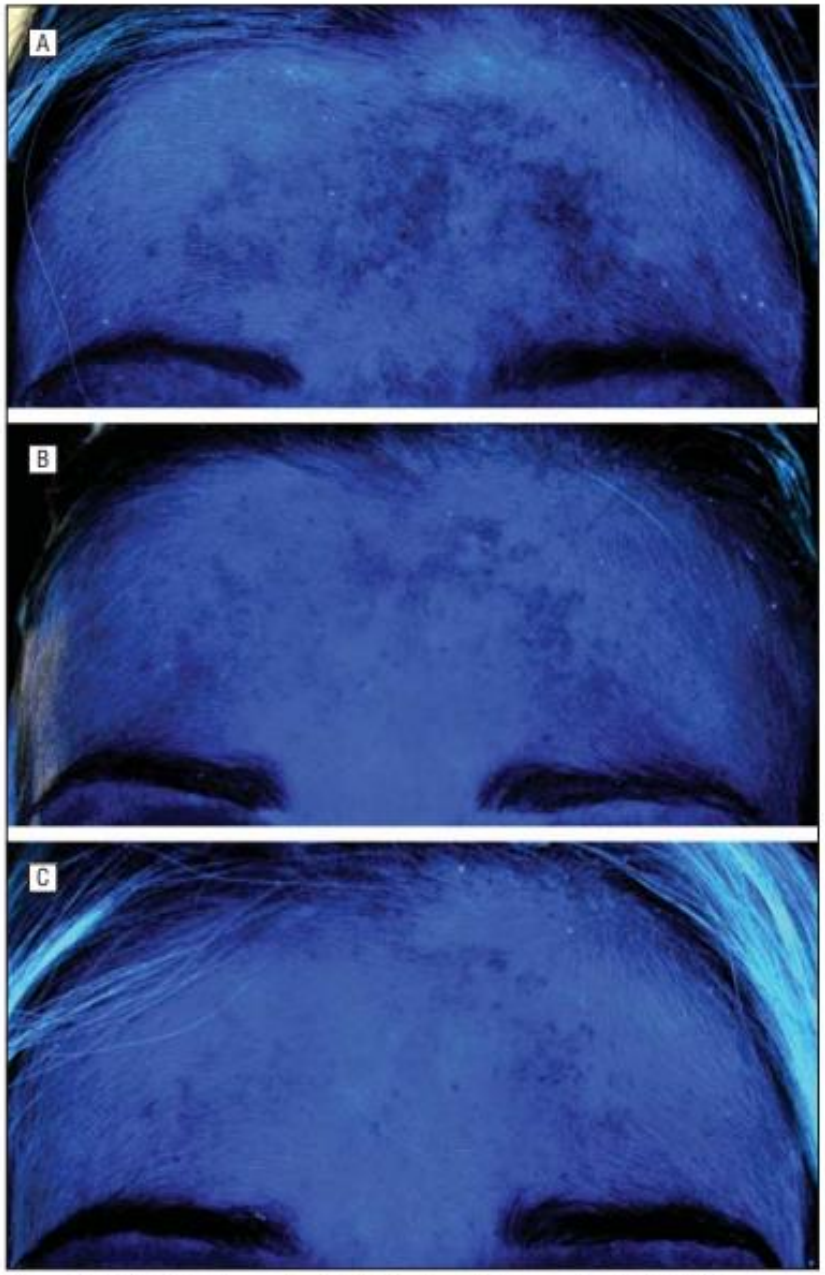


Figure. Clinical photographs of the forehead taken under UV light before treatment (A), at the end of the treatment (B), and after 1 summer (C). Left side of the patient's face has been treated with the triple combination cream, right side with both the cream and pulsed-dye laser.

Maintenance

- **The reverting nature of melasma emphasizes the importance of maintaining efficacy achieved after triple combination treatment**.
- Kligman and Willis, the founders of a similar composition of TC therapy, observed that melasma relapse started as early as 1–2 weeks after cessation of treatment.
- The maintenance regimens could postpone melasma relapse by almost 5 months compared to the conventional cessation of daily.

Maintenance

➢Regime 1

- A study conducted by Arellano et al. (2012) demonstrated the **twice-weekly** triple combination regimen for **4 month** was more effective with a lower relapse on mild melasma, while the **tapering regimen (3 / week – 1st month, 2 / week –2nd and 3rd month, 1 / week – 4th month)** was more appropriate for those with moderate melasma.
- The result also confirmed that applying triple combination intermittently over a long time period is tolerable, safe and improver of the patient's quality of life.

Maintenance

➢ **Regime 2**

- Grimes et al. in 2010 wrote that: Suggested maintenance regimen comprises 4% hydroquinone, tretinoin 0.05% and fluocinolone acetonide 0.01% applied twice weekly for 12 weeks.
- Wang et al. in 2019 said that: Triple combination was **applied daily for 8 weeks**, and in case of skin irritation, patients were allowed to **taper down to twice weekly in the following 6 weeks** and **once weekly in the final 6 weeks until** the final evaluation at **week 20**.

Side-effects of combination treatment

- ✓Erythema
- ✓Irritation
- ✓pruritus
- ✓Desquamation
- ✓cost

In a study by Kandhari and Khunger,[11] 69 patients with melasma were allocated to different combinations of tretinoin, corticosteroids and hydroquinone, individually and in combination, for varying durations. Erythema was reported in 43 patients (due to irritancy of hydroquinone), hypertrichosis in 30, telangiectasia in 25, acneiform eruptions in 18, rosacea-like-eruption in 13, epidermal atrophy in 2 and irritant contact dermatitis in 1 patient.[11] Sodium metabisulfite is a preservative found in hydroquinone formulations, which can cause hives, itching, wheezing, anaphylaxis and asthma exacerbations in susceptible individuals.[12]

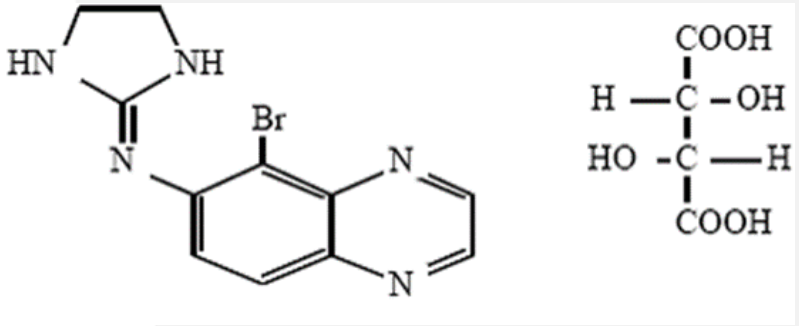
➢ these side effects were transient and mild

Solution

- ✓Using a moisturizer in the morning
- ✓Using a sunscreen (SPF >30) during the day
- ✓Using a mild cleanser


Janu-brim®
For the Facial Erythema of Rosacea
For External use only
Janu-brim® 0.33%
Brimonidine
Each 100 gr contains:
Brimonidine tartrate) 0.33g
Topical Gel
Janu-brim® 0.33%
Brimonidine
The first FDA-approved topical treatment for
the persistent facial erythema of rosacea

Introduction



- Brimonidine topical gel, 0.33% contains brimonidine tartrate.
- Each gram of brimonidine topical gel, 0.33% contains 5 mg of the active ingredient brimonidine tartrate (equivalent to 3.3 mg of brimonidine free base), in a white to light yellow opaque gel

Mechanism of Action

- Brimonidine is a relatively selective alpha-2 adrenergic agonist. Topical application of brimonidine topical gel may reduce erythema through direct vasoconstriction

Pharmacokinetics

Absorption

The absorption of brimonidine from brimonidine topical gel was evaluated in a clinical trial in 24 adult subjects with facial erythema associated with rosacea.

All enrolled subjects received once daily topical application of brimonidine topical gel 1 gram to the entire face for 29 days. Pharmacokinetic assessments were performed on Day 1, Day 15, and Day 29.

The mean plasma maximum concentration (Cmax) and area under the concentration-time curve (AUC) were highest on Day 15.

The systemic drug exposure was slightly lower on Day 29 indicating no further drug accumulation.

- پاسخ به درمان معمولا بعد از گذراندن ۵ روز از دوره مصرف، آغاز می شود.
- دارو را روزانه به اندازه ی یک نخود به طور یکنواخت و به صورت یک لایه نازک بر روی موضع مورد نظر (پیشانی، چانه، بینی و گونه ها) بمالید.
- مقدار داروی مورد استفاده در روز نباید بیش از یک گرم باشد.
- از استعمال این دارو بر روی پوست تحریک شده و یا زخم های باز خودداری نمایید.
- از تماس دارو با چشم ها و دیگر سطوح مخاطی (دهان و بینی) جدا اجتناب نمایید.
- این دارو در رده B قرار دارد.
- ژل موضعی بریمونیدین یک درمان علامتی بوده و بعد از اینکه اثر دارو از بین رفت، قرمزی برمی گردد.
- بعد از خشک شدن ژل بر روی پوستتان میتوانید از کرم های آرایشی استفاده نمایید.

CLINICAL STUDIES

- Brimonidine topical gel was evaluated for the treatment of moderate to severe, persistent facial erythema of rosacea in two randomized, double-blind, vehicle-controlled clinical trials, which were identical in design. The trials were conducted in 553 subjects aged 18 years and older who were treated once daily for 4 weeks with either brimonidine topical gel or vehicle.
- Baseline disease severity was graded using a 5 point Clinical Erythema Assessment (CEA) scale and a 5-point Patient Self Assessment (PSA) scale, on which subjects scored either “moderate” or “severe” on both scales.
- The primary efficacy endpoint in both trials was 2-grade Composite Success, defined as the proportion of subjects with a 2-grade improvement on both CEA and PSA measured at hours 3, 6, 9, and 12 on Day 29.

Table 2: Summary of 2-grade Composite Success on Day 29

Success	Study 1		Study 2	
	MIRVASO Topical Gel (N=129)	Vehicle Gel (N=131)	MIRVASO Topical Gel (N=148)	Vehicle Gel (N=145)
Hour 3	31%	11%	25%	9%
Hour 6	30%	10%	25%	9%
Hour 9	26%	10%	18%	11%
Hour 12	23%	9%	22%	10%

2-grade Composite Success: 2-grade improvement on CEA and 2-grade improvement on PSA.

Figure 1: 2-grade Composite Success by Hour and Day for Study 1

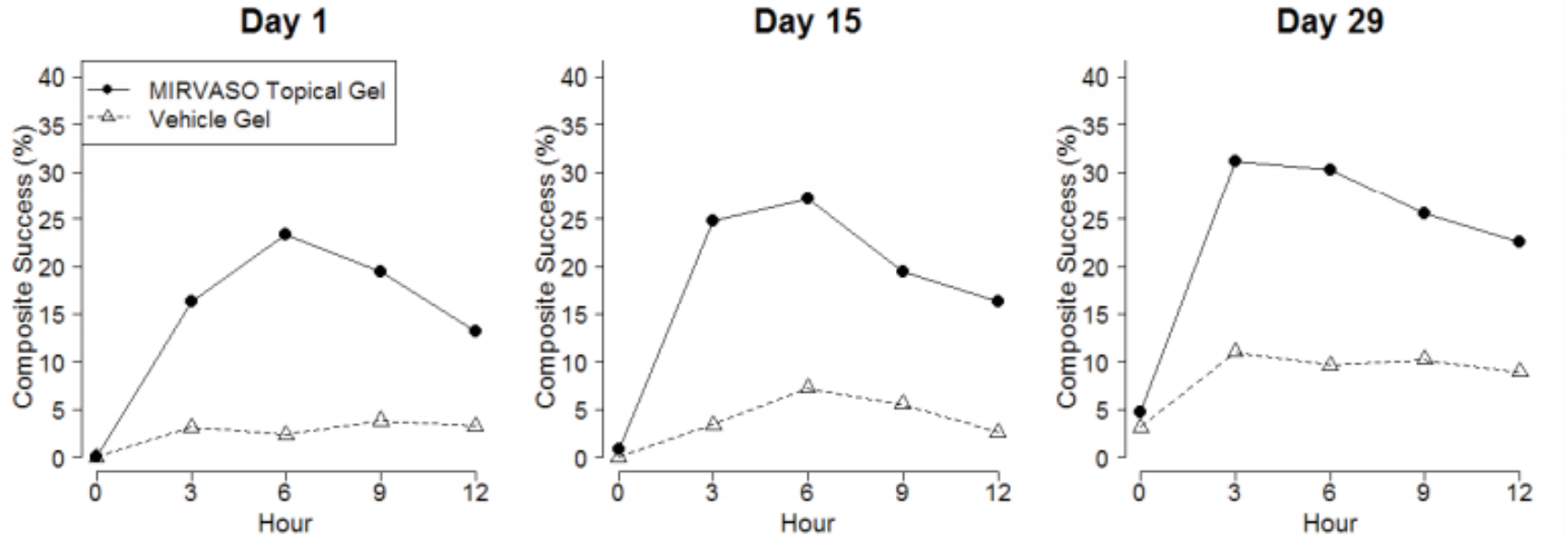
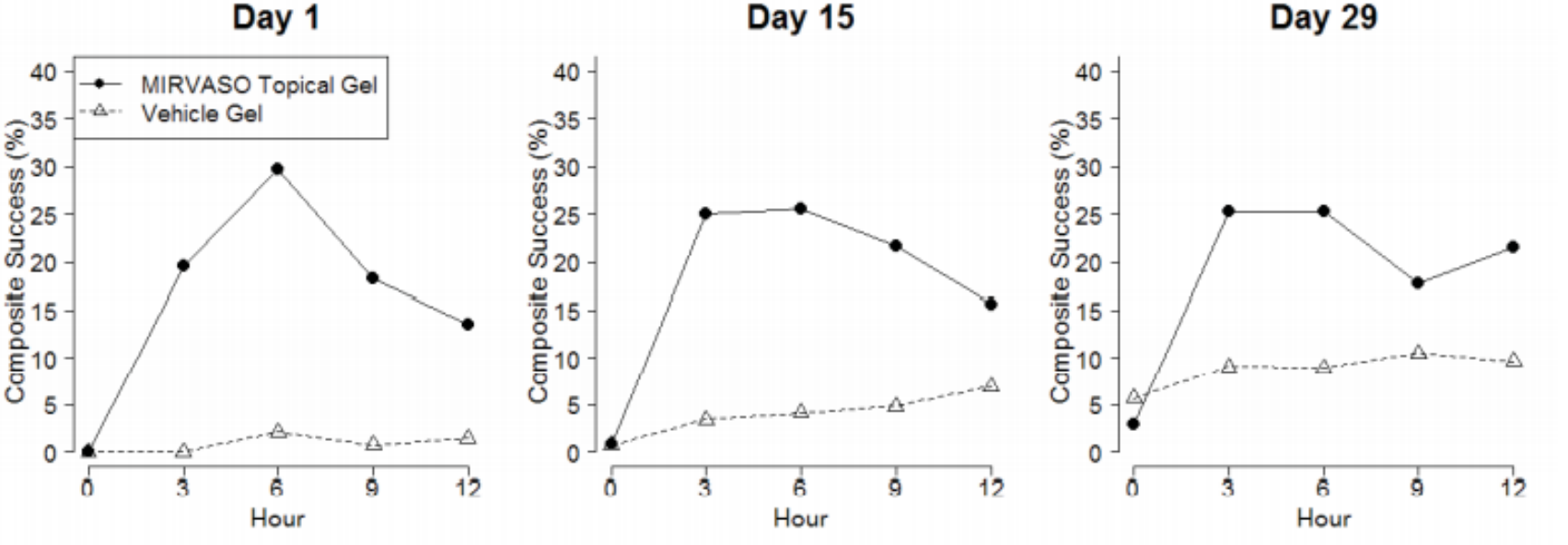


Figure 2: 2-grade Composite Success by Hour and Day for Study 2



Adverse reactions

- In controlled clinical trials with brimonidine topical gel the most common adverse reactions (incidence ≥ 1%) included
- erythema
- flushing
- skin burning sensation
- contact dermatitis

Table 1 - Adverse Reactions Reported in Clinical Trials by at Least 1% of Subjects Treated for 29 Days

Preferred Term	MIRVASO Topical Gel (N=330) n (%)	Vehicle Gel (N=331) n (%)
Subjects with at least one adverse reaction, Number (%) of Subjects	**109 (33)**	**91 (28)**
Erythema	12 (4%)	3 (1%)
Flushing	9 (3%)	0
Skin burning sensation	5 (2%)	2 (1%)
Dermatitis contact	3 (1%)	1 (<1%)
Dermatitis	3 (1%)	1 (<1%)
Skin warm	3 (1%)	0
Paraesthesia	2 (1%)	1 (<1%)
Acne	2 (1%)	1 (<1%)
Pain of skin	2 (1%)	0
Vision blurred	2 (1%)	0
Nasal congestion	2 (1%)	0

For Dermatitis Treatment

Website: www.januspharma.com
Email: headoffice@januspharma.com

شرکت دانش بنیان ژرف اندیشان نوید سلامت (ژانوس)
تهران، خیابان طالقانی، نبش خیابان شهید نادری، شماره ۴۱۵
تلفن: ۸۸۹۶۲۹۸۱ فکس: ۸۸۹۶۲۶۵۲

Desonide

- Desonide is a synthetic, nonflourinated, low-potency corticosteroid that has been used to treat inflammatory, steroid-responsive dermatoses for over 30 years.
- safety profile of this topical agent makes it ideal for patients of all ages.
- Traditionally, only creams, ointments and lotions were available in this potency class; recently, however, novel hydrogel and foam formulations of desonide have been developed.
- These advancements in vehicle technology address the need for effective, well-tolerated treatments, and may enhance patient compliance and acceptability.
- Pregnancy category: C

Indication

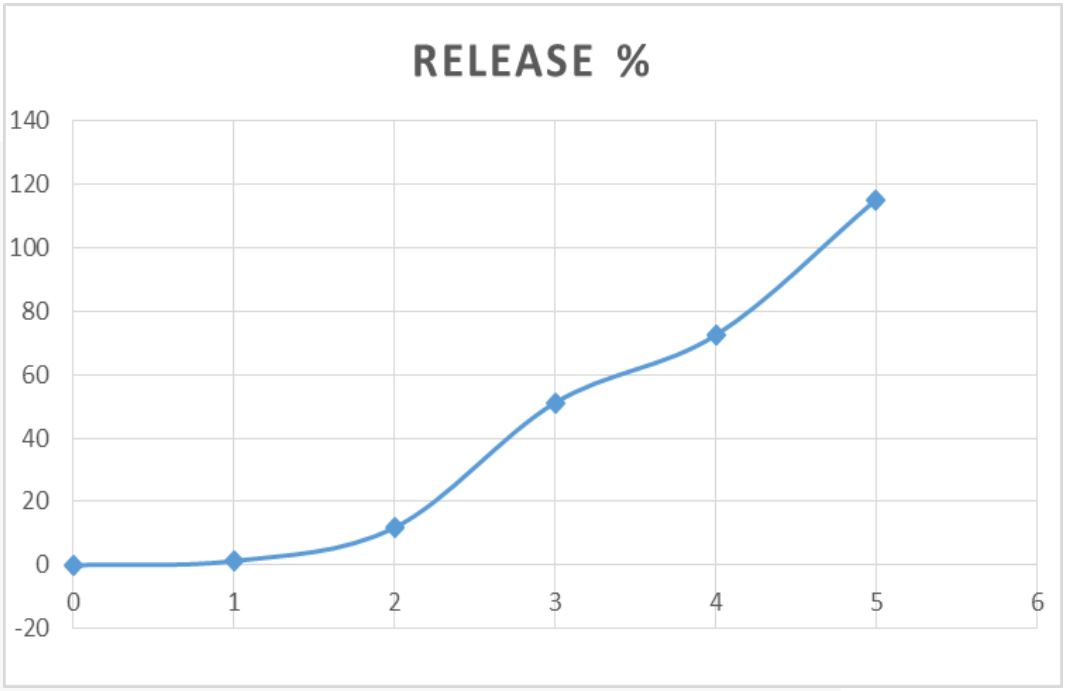
- **Desonide is a Class VI, low-potency corticosteroid used for the treatment of atopic dermatitis, seborrheic dermatitis, contact dermatitis, psoriasis, eczema and other steroid-responsive dermatoses.**
- **Like most topical corticosteroids, desonide has been shown to have anti-inflammatory, antipruritic and vasoconstrictive properties**

Antipruritic

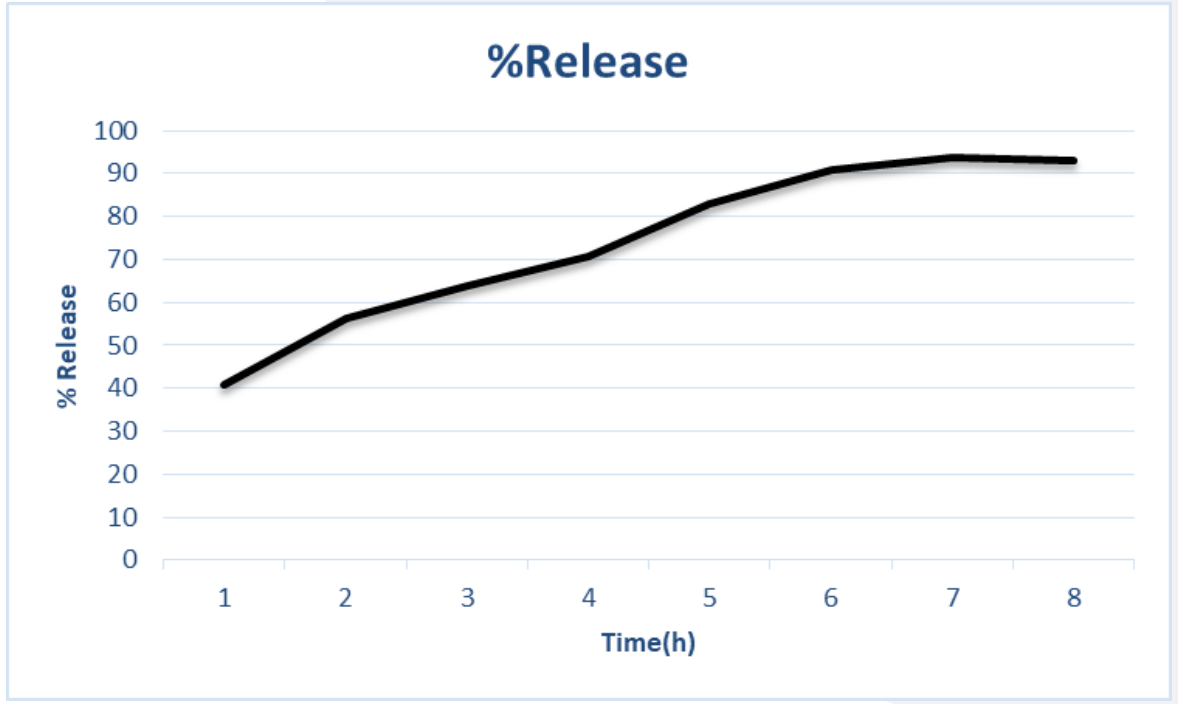
- Recent studies have demonstrated a rapid improvement of pruritus in pediatric patients using desonide. Two randomized, vehicle-controlled studies involving 582 children with atopic dermatitis demonstrated marked improvement in pruritus after 4 weeks of twice-daily desonide hydrogel application.
- Pruritus scores in the desonide group decreased from 76% at baseline to 12% following 4 weeks of treatment.
- The vehicle group only showed a decrease from 69% at baseline to 41% after treatment

Pharmacokinetics and absorption

- **Several factors affect the pharmacokinetics of topical corticosteroids. The molecular structure, the vehicle used for delivery and the state of the patient's skin at the site of application all play important roles in the overall efficacy of the medication.**
- **Most topical steroids share a hydrocortisone backbone, and their differences lie in the addition or alteration of various functional groups or double bonds. These subtle changes can have significant impact on the absorption and activity of the molecules.**



نتایج حاصل از آزادسازی ماده موثره دزوناید از ژل موضعی ژانوناید در زمان‌های مختلف بر حسب ساعت

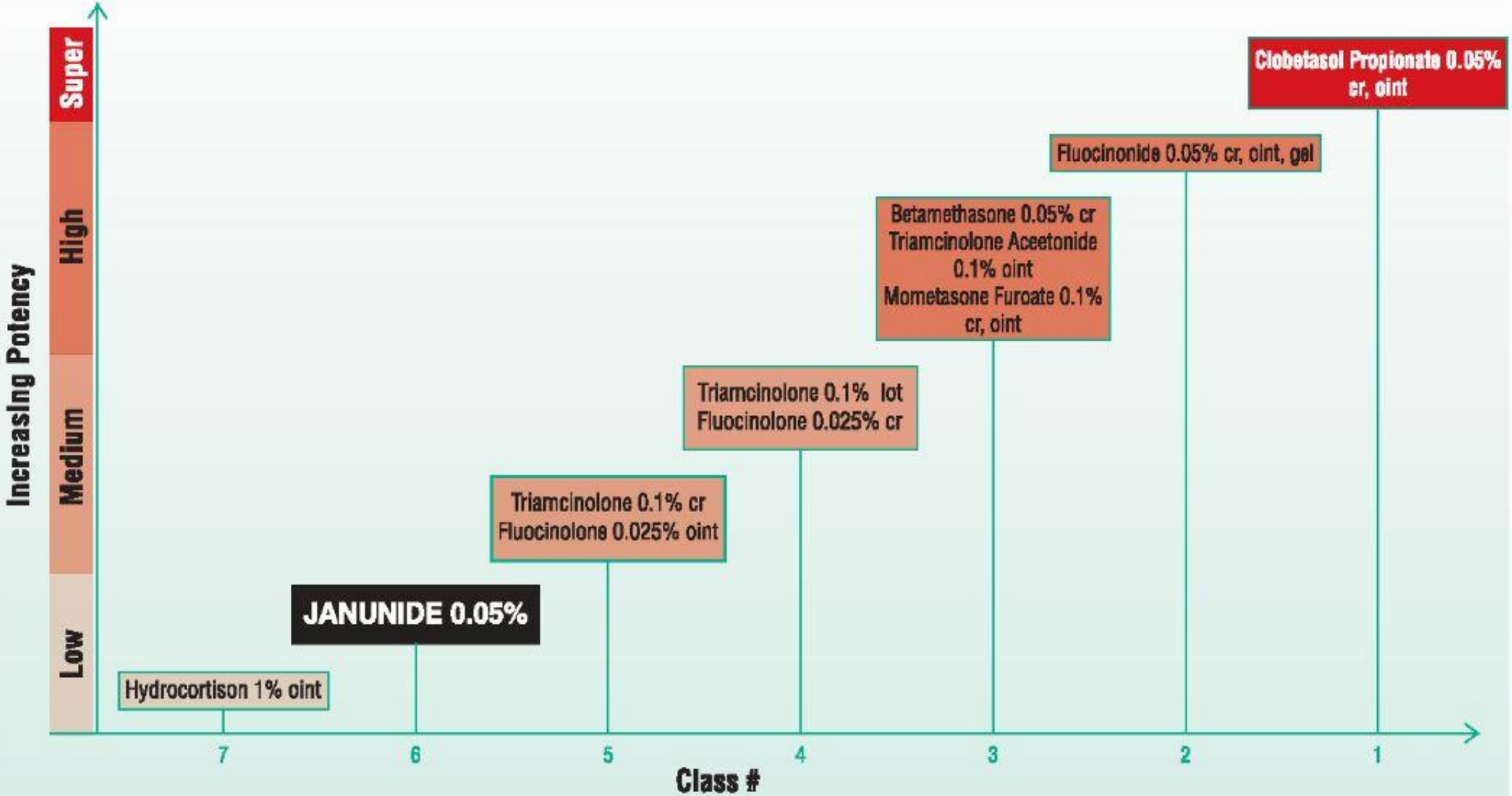


نتایج حاصل از آزادسازی ماده موثره دزوناید از پماد موضعی ژانوناید در زمان‌های مختلف بر حسب ساعت

Formulation

- Desonide comes in ointment, cream, lotion, gel and foam formulations
- Desonide, the active ingredient, has a molecular weight of 416.52 kD
- is a white, odorless powder that is practically insoluble in water, sparingly soluble in ethanol and in acetone, and soluble in methanol and chloroform

مقایسه قدرت استروئیدی ژانونواید



Factors to consider when choosing a topical preparation

- **Always consider the effect of the vehicle. An occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient, or protective action. It can also cause side effects by being excessively drying or occlusive.**

- **Match the type of preparation with the type of lesions. For example, avoid greasy ointments for acute weepy dermatitis.**

- **Match the type of preparation with the site (e.g., gel or lotion for hairy areas).**

- **Consider irritation or sensitization potential. Generally, ointments and w/o creams are less irritating, while gels are irritating. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.**

Atrophy

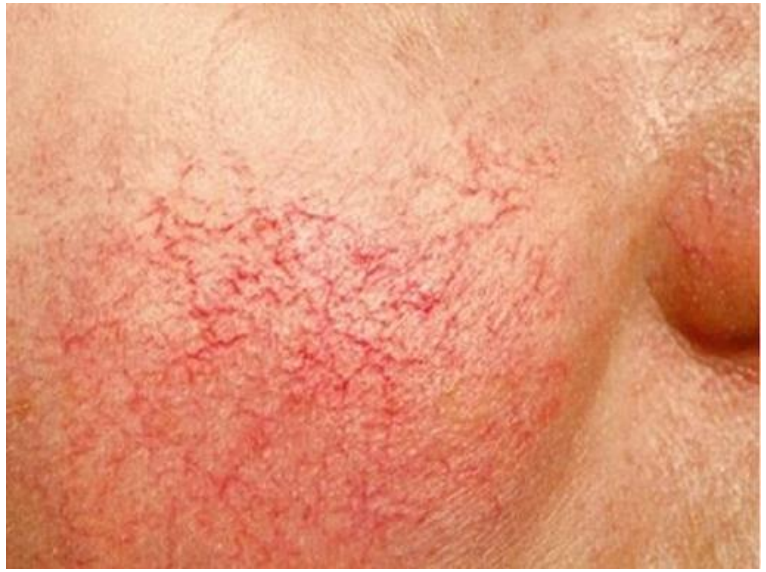
- **Jorizzo *et al. (*113 patients*)* found that children using desonide 0.05% ointment twice daily showed no signs of cutaneous atrophy after 5 weeks of treatment.**
- **In a study by Hebert, there were no reported cases of skin atrophy in 425 subjects treated with desonide hydrogel**

Burning

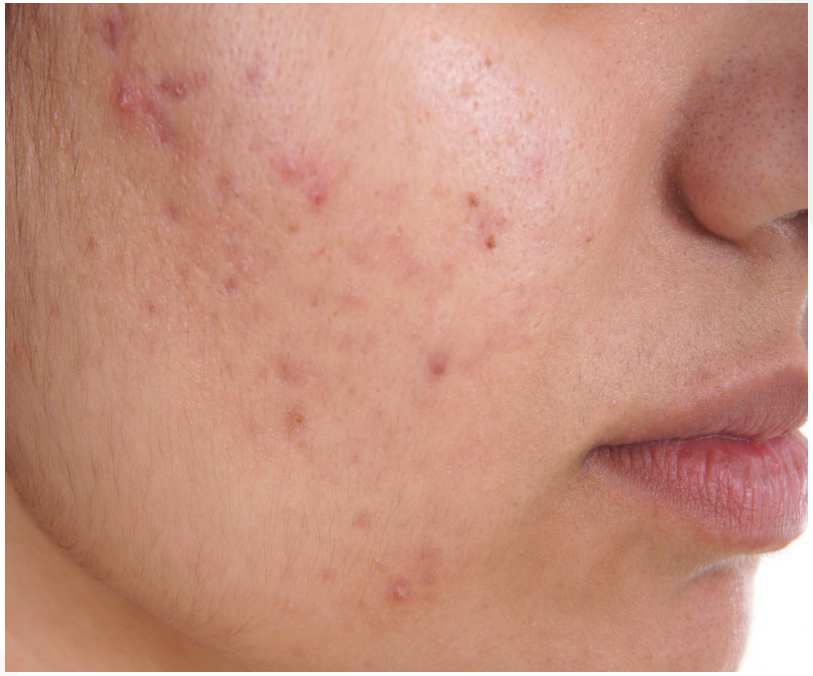
- **Jorizzo *et al.* (113 patients) report that any stinging or burning sensations noted in their study were slight.**
- **In the study by Hebert, the incidence of application-site burning was 1% in the desonide hydrogel group, which was not higher than that reported in the vehicle group**

Telangiectasia

- **A single case in which telangiectasias appeared at the application site was reported in the study by Hebert (425 patients)**



Acne



- **One case report of acne associated with desonide use was identified. A 2-year-old girl developed topical corticosteroid induced acne after using a regimen of clotrimazole 1%, betamethasone 0.05% cream and desonide 0.05% cream**

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