

CORE TUTORIALS IN DERMATOLOGY FOR PRIMARY CARE

ACNE

PICTURE SHOWING SUBMARINE
EXTENT OF ICEBERG



UPDATED CHAPTER
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Inspect the skin to establish the extent
of 'submarine' comedones

CORE TUTORIALS IN DERMATOLOGY FOR PRIMARY CARE

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Acne, unarguably, is ‘core’ clinical material in dermatology for primary care physician and specialist alike. It affects to some degree 85% of adolescent females and 95% of males,¹ although it is only considered ‘clinically significant’ in approximately 15%. The age of onset is approximately 12 years with peak severity at 14-17 in females and 16-19 in males. It would be a misperception however to consider this purely a disease of adolescence with studies reporting a significant incidence in adult life.²

PATHOGENESIS OF ACNE

It is essential to have a good grasp of the pathogenesis of acne in order to treat it effectively. Although the detail remains unclear, it is sufficient to understand the condition as a complex interplay of androgen hypersensitivity, ductal hypercornification and occlusion, bacterial colonisation and subsequent activation of inflammatory mediators leading to a chronic inflammatory process in the pilosebaceous unit. Bacteriologically, *Cutibacterium acnes* (*C. acnes*), formerly known as *Propionibacterium acnes* (*P. acnes*) is the main player.

The diagnosis of acne rarely poses problems to the physician. However, one should be able to demonstrate the presence of both comedones and papules/pustules. The earliest expression of the disease process is the microcomedone; mid-facial comedones may pre-date inflammatory acne by several years. Subsequent lesions which must be confidently differentiated by the physician are both closed and open comedones (white and blackheads), papules, pustules, nodules and a variety of scars, atrophic, ice-pick and hypertrophic/keloid. It is the recognition of the ‘lesion mix’ that determines both the potential severity of the acne and the rationale for individually tailored treatment regimes.



HYPERTROPHIC/KELOID SCARS

Keloid Scars – Elevated, surface smooth and pink with irregular shape.



ATROPHIC MACULAR SCARS

Atrophic Macular Scars – Depressed 5-20mm diameter, typically red or violaceous.

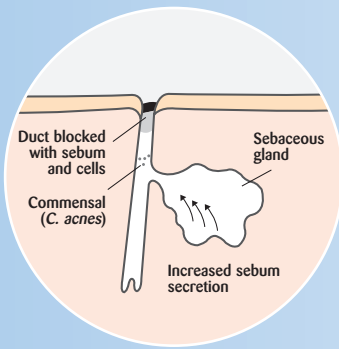


ICE PICK SCARS

Ice Pick Scars – Small, superficial to deep with well defined edge.



COMEDONAL ACNE



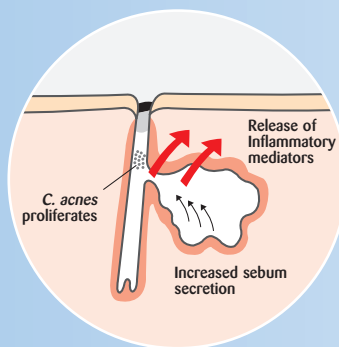
Excess sebum, and cells shed from the lining, block the duct and form a plug:

- below the surface – **whitehead**
- at the surface – **blackhead** (sebum/cellular mix turns black in air)

COMEDONES



INFLAMMATORY ACNE



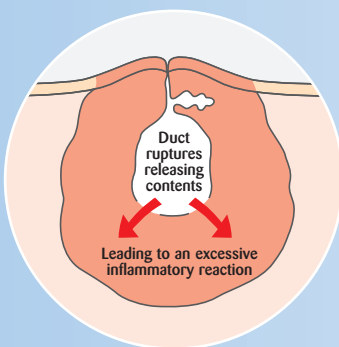
Proliferation of normally harmless skin commensal, *C. acnes*, causes breakdown of sebum which triggers an inflammatory response resulting in:

- Papules – inflamed pimples
- Pustules – spots containing pus (inflammatory response debris)

PAPULES AND PUSTULES



NODULAR OR CYSTIC ACNE



The most severe type of acne lesion. Rupture of the duct wall releases follicular contents into the surrounding skin, leading to more inflammation, pain and swelling. Nodules extend deep into the area that contains the skin's structural support, and the tissue damage leads to scarring.

NODULES



Occasionally there can be diagnostic confusion with

1) **Rosacea**; (previously called acne rosacea; this term is now strongly discouraged to avoid any confusion as rosacea is not a follicular disorder, the disease process is entirely different). Differentiating features are a history of flushing, the presence of telangiectasia and the absence of comedones.

ROSACEA



2) **Perioral/periorbital dermatitis**; this produces a characteristic pattern of monomorphic itchy pustules around the mouth with immediate circumoral sparing. This condition also rarely occurs around the eyes. It characteristically affects young women and there is a very strong association with the use of topical steroids which exacerbate the condition.

PERIORAL DERMATITIS



3) **Gram negative folliculitis**; this may be suspected, if the acne is acutely pustular and monomorphic in appearance and unusually resistant to treatment. Liaison with your local microbiologist will be useful. This condition constitutes consideration for referral.

4) **Drug induced acne**; examples would be phenytoin and steroids. Acne induced by anabolic steroids, either therapeutic or illegal, produces a picture of monomorphic acneiform lesions and absence of comedones.

Acne can also be clinically evident in babies where the appearances are typical but the age of the patient creates diagnostic doubt. Up to 20% of neonates will have transient acneiform rashes. The aetiology is thought to be sensitisation to maternal androgens. Endocrinological investigation is only necessary if there are other features of androgenisation or precocious puberty. Treatment is along conventional lines with topical agents.

It is my experience that in this modern, iconic, media driven society that the threshold for seeking advice about acne is dropping. This is particularly true in relation to the prescribing of systemic retinoids which remain only available through specialists at present. Indications for specialist referral will be discussed later.



Before we progress any further we must be aware that there may be a significant delay before a patient consults us as a consequence of their acne. I feel therefore, particularly in the vulnerable adolescent age group where communication can often be challenging, that we as doctors be prepared to raise the issue of acne and its treatment opportunistically. I have done this on many occasions over the years and if done tactfully, especially if you have already an established relationship with a patient, the interest is well received and not resented.

Thereafter the consultation should

1. ESTABLISH that although there is no ‘cure’ there is effective treatment for all grades of acne.

The opportunity must be taken to explode the common associated myths. There is no link between chocolate, chips (parents often hate me for this) or lack of cleanliness. Blackheads are a result of oxidation of sebum **not** poor hygiene.

2. ASSESS the clinical picture – this requires a holistic approach.

History should include any evidence of severe and scarring acne in older siblings or parents, and also a history of treatments already tried.

The severity and the extent of the acne must be established. Is the clinical picture today representative? Acne can be very variable in the same individual.

The skin must be inspected, but stretching and palpation is also often needed to establish the depth of lesions, the extent of scarring and the presence of ‘submarine’ comedones networking beneath the skin surface.

All acne prone areas should be examined – often mild facial involvement may coexist with a ‘lunar landscape’ of a back and vice versa. The anterior chest is also cosmetically very vulnerable. Adolescents may be reticent about a more extended examination but a complete assessment cannot otherwise be made. Truncal acne is generally more resistant to treatment and topical treatments are logistically challenging. Physical exam can also help defuse feelings of infectiousness and uncleanliness.

There exist many scales for the grading of severity. There is however a lack of consensus and objective evidence regarding their use. Historically the most established is the Leeds grading scale developed by Prof W Cunliffe *et al.*³ NICE guidelines published for Acne for the first time in June 2021 have defined 2 grades of acne:⁴

Mild to moderate:

- Any number of non-inflammatory lesions (comedones)
- Up to 34 inflammatory lesions (with or without non-inflammatory lesions)
- Up to 2 nodules

Moderate to severe:

- 35 or more inflammatory lesions
- 3 or more nodules

Some might prefer not to use such an unwieldy “lesion counting” tool but the important point to note is to have some form of objective measurement on which to monitor progress and base future management decisions.

More sensitive still may be the psychological assessment of the impact of acne on the individual. This must never be underestimated and often correlates poorly with objective measures of severity. Acne is a cruel condition that largely afflicts a vulnerable age group. I was struck once during a presentation from a representative of the Acne Support Group when she said that if she wore a tee shirt spelling 'ACNE', it would spell 'UGLY'! Research has established unequivocally that significant acne can lead to long term social disability, both in terms of employment, and establishing and maintaining relationships.² Often an accompanying parent can give a clear insight into how acne is impacting on the patient. Formal quality of life questionnaires such as DLQI/CADI can also be used.

Other issues that need to be addressed include advice on skin care using non-alkaline skin cleansers, avoiding oil-based comedogenic cosmetics and resisting scratching and picking. In female patients where contraception is required, advice to use combined rather than progesterone only contraceptives should be given. There is presently insufficient evidence to suggest any specific dietary alterations but smoking may exacerbate acne!⁵

TREATMENT

There is an often baffling array of options available but fundamentally with the exception of isotretinoin (Roaccutane), each treatment individually addresses only one or sometimes two of the aetiological factors thought to be involved in acne, and this must be constantly kept in mind when designing treatment regimes. Just as we treat hypertension often with drugs directed at different aspects of the condition, so must we with acne. The available treatments are broadly classified below, with explanatory notes as required, followed by the important principles of management which is incorporated into the current NICE guidance.⁴



TOPICAL PREPARATIONS

Benzoyl Peroxide

- A mainstay of topical treatment since the 1930's
- Works predominately as an antimicrobial by virtue of oxidisation of anaerobic *C. acnes*, therefore most useful for inflammatory acne with the presence of papules/pustules; can produce a profound reduction in surface bacteria counts (x 100 fold)
- Mode of action does not allow resistance to develop
- Available in a variety of strengths from 2.5% - 10%, and presentations – gel, cream or wash. I do not advocate strengths greater than 5% as there is no evidence of greater efficacy of the stronger concentrations over the weaker ones⁶
- Main side effects are irritancy and bleaching
- Use as daily or twice daily regimes
- Available over the counter

Topical Retinoids

- Synthetic Vitamin A derivatives
- Indicated for treatment of comedonal acne. Most effective against open comedones, but regular treatment may prevent progression of the microcomedone and consequently decrease subsequent acne severity. As comedones play a pivotal role in the pathogenesis of acne, such preparations should be included in the treatment regimes of most affected patients unless contra-indicated/not tolerated but this does not always appear to happen!
- Available in cream and gel preparations in various strengths which should be matched to the patient's skin type and a lower strength used first. Patients must be warned that the skin may take time to develop tolerance
- Usually used as a once daily regime, applied at night to reduce the risk of photosensitivity
- All these preparations are advised to be avoided in pregnancy despite lack of evidence of any systemic absorption due to the association with oral isotretinoin and its profound potential for teratogenicity
- Available as
 - adapalene
 - tretinoin (combined products only)

Azelaic Acid

- Has therapeutic effects both as an antimicrobial and anticomedonal agent
- Usually used as a twice daily regime
- Well tolerated
- Available as 15% and 20% strengths

Nicotinamide

- Vitamin B₃ derivative
- Active against inflammatory acne
- Similar in efficacy to topical antibiotics but with no risk of resistance⁷

Topical Antibiotics

- Antimicrobial and ? anti-inflammatory as can still be effective in the presence of proven bacterial resistance
- No evidence of greater efficacy of any one preparation in this class. There is a desperate need for good 'head to head' clinical trials
- Often more expensive to treat with topical antibiotics than systemic antibiotics but preparations generally well tolerated
- No direct evidence that topical antibiotics are less effective than systemic antibiotics when used as monotherapy
- Preparations available:
 - clindamycin
 - erythromycin (combined product only)

Over the last few years a number of fixed combination preparations have become available which combine topical antibiotics with retinoids, zinc or benzoyl peroxide. There is evidence of greater efficacy with combination treatments of benzoyl peroxide with both clindamycin and adapalene. The latter may be a logical combination as this may counteract increasing resistance from *C. acnes*.

Examples of combination treatments currently available:

- Adapalene & benzoyl peroxide gel
- Tretinoin & clindamycin gel
- Tretinoin & erythromycin solution
- Benzoyl peroxide & clindamycin gel
- Erythromycin & zinc acetate topical solution

SYSTEMIC PREPARATIONS

Systemic Antibiotics

- Lymecycline capsules 408mg once daily
- Doxycycline 100mg daily
- Oxytetracycline – suggested regime 500mg twice daily
- Erythromycin 500mg twice daily
- Trimethoprim 200mg twice daily

NB: Trimethoprim does not presently hold a licence for acne treatment but can be very effective.

NICE guidance regarding strategies for use of this therapeutic armamentarium are as follows:

First line: fixed topical combination products containing either a retinoid/benzoyl peroxide or azaleic acid according to tolerance/safety.

Addition of oral or topical antibiotic preferably once daily preparations to enhance compliance. Use lymecycline or doxycycline first line and erythromycin/trimethoprim as second line.

N.B. topical products difficult to use logistically in widespread truncal acne.

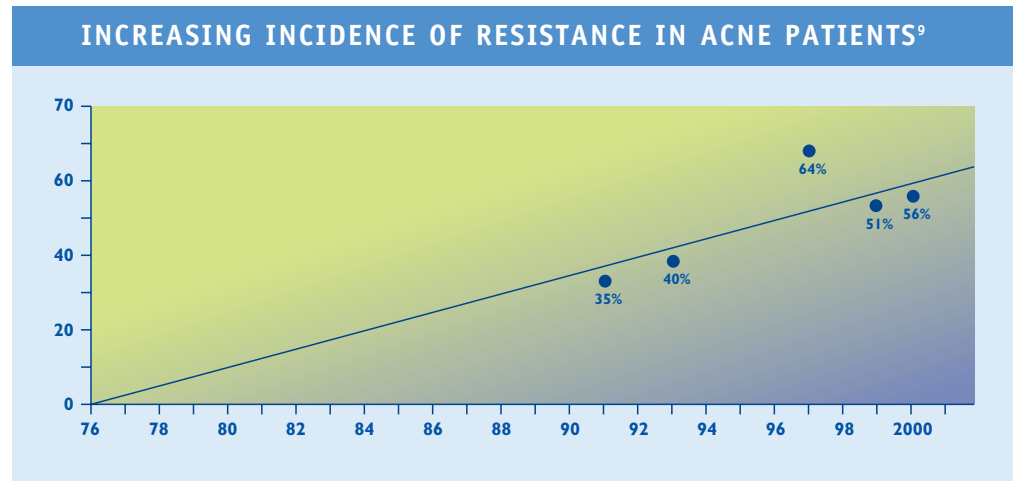


Systemic antibiotics should be used for moderate to severe acne in combination with non antibiotic topical treatments, or when topical treatments alone are not sufficient, or for more severe acne whilst awaiting specialist opinion. Courses must be at adequate dosage as illustrated above and be carried on for 12 weeks before review. Full dosage can be continued thereafter for a further 12 weeks if required. Treatment can then be discontinued or a topical maintenance regime introduced according to response on an individual case by case basis. Treatment regimes should be regularly assessed thereafter. Further cycles can be considered if the treatment has been effective. It is recommended that any subsequent cycles should use the same antibiotic.

During both pregnancy and risk of pregnancy, retinoids, both oral and topical and tetracycline antibiotics **must be avoided**.

Antibiotic Resistance

In vitro studies demonstrate alarming rates of resistance of *C. acnes* to antibiotics in common usage. Resistance to erythromycin has been recorded as high as 60%-70%. A UK systematic review suggests current rates of 50% resistance to topical macrolide antibiotics⁸ and a study in 1996 demonstrated 25% of all community *C. acnes* was resistant to one or more of the commonly used drugs.



There is clear evidence that the presence of resistance reduces efficacy, especially in the case of erythromycin but this, however, does not completely negate the clinical benefit of both topical and oral antibiotics. These preparations are also working in other ways and indeed the tetracycline class of antibiotics has established anti-inflammatory action, and is used in a wide range of dermatological conditions for this very reason. Antibiotic resistance patterns of *C. acnes* are not routinely available so a clinical judgement about lack of response must be made. It is important to note that most tetracycline resistant strains demonstrate cross resistance to doxycycline, and the same is true of erythromycin and clindamycin.

Minocycline has previously attempted to justify its much greater expense on the basis of convenience leading to enhanced compliance, and also its track record for low resistance which has been reported as less than 1% in the UK. However, resistance rates of up to 20% have been reported in the USA, and in addition as minocycline is unstable in bacteriological culture, measurement of resistance can be unreliable. There is no evidence that minocycline is any more effective than the traditional cheaper options. Although all the antibiotics used in the long term treatment of acne are generally very well tolerated, minocycline does have the risk of significant but rare side effects including hepatitis, a lupus like syndrome, benign intracranial hypertension and a blue-grey pigmentary disturbance of the skin which can be quite persistent. Some authorities recommend regular blood monitoring with liver function, ANF (antinuclear factor) and ANCA (antineutrophil cytoplasmic antibody).

There are now some generally agreed 'best practice' guidelines to try to reduce the risk of resistance in antibiotics used in acne.

"BEST PRACTICE" GUIDELINES TO REDUCE ANTIBIOTIC RESISTANCE

- Do not prescribe antibiotics if a non antibiotic topical preparation will do
- Do not use antibiotics as monotherapy either topically or systemically
- Do not continue treatment for longer than six months at any one time
- If further treatment is required, reuse the same drug; short intervening courses of a topical antibacterial such as benzoyl peroxide may help eradicate resistant organisms
- Avoid concomitant oral and topical treatment with antibiotics



Hormonal Treatments

Co-cyprindiol (Dianette) – this combined preparation consists of cyproterone 2mg and ethinyloestradiol 35mcg.

- It has historically been the mainstay of hormone manipulation in menstruating women with resistant acne
- It works primarily as an anti-androgen as a consequence of the cyproterone, and its primary action is to reduce sebum production. The average reduction is 30% and 80% of patients show improvement after 3 months continuous treatment
- There is no clear comparative data of safety/tolerability/outcomes available for anti-androgens versus other systemic treatments¹⁰
- It is also an effective contraceptive but has no licence as such. An additional hormonal contraceptive should not be used in combination with co-cyprindiol¹¹
- It is a very effective adjunct to therapy, particularly in women in their 20's and 30's with low grade grumbling acne who also require effective birth control
- Remains a useful treatment in women diagnosed with polycystic ovarian syndrome (PCOS)
- Contraindications are the same as the combined oral contraceptive pill. There may however be a slightly higher risk of thromboembolism and patients should be counselled regarding this¹¹
- Previous guidelines suggest continuous use should be restricted to 6 months but there are no problems continuing for longer periods, as there is good data that supports a safety profile for up to 5 years of continuous use.¹² The clinical response should be reviewed periodically¹¹
- Use should be discontinued 3 months after acne is controlled

Some oral contraceptive pills are considered to be less androgenic and therefore 'acne friendly'. These contain the newer synthetic progestogens while more established pills contain levonorgestrel and norethisterone, which may have a negative effect.

Cyproterone can be used as a single agent as an anti-androgen and spironolactone also has similar effects; neither of these should be considered routinely for acne and should be reserved for specialist use. This would also be true for other second line drugs such as dapsons.

It is recognised that there has been a recent upsurge in more mature women presenting with acne. The explanation is thought to be the increasingly widespread use of long-acting progestogen contraceptive devices, such as, Nexplanon and Mirena.

ULTRAVIOLET LIGHT

This has only a transient benefit for acne and should not be considered therapeutically. Photodynamic treatment remains the remit of the specialist.

PHYSICAL TREATMENTS

A variety of physical methods for the treatment of post acne scarring can be effective, including laser resurfacing, dermabrasion, chemical peels and collagen injections, but these are rarely easily accessible under the NHS. Emphasis should always be on avoiding scarring in the first place.

Acne nodules which are also wrongly described as 'cysts' and post acne keloid scarring can benefit from infiltration with triamcinolone 10mg/ml in someone trained in how to administer this treatment which remains off-label.

Acne cyst before and after infiltration with triamcinolone 10mg/ml



Suitably armed with a myriad array of treatments, we now have assessed the type, severity, distribution and psychopathology of our patient and are in a position to select a suitable regime guided by the treatment algorithms incorporated into NICE guidance. A pragmatic and realistic target, broadly speaking, would be to reduce the lesions by 50% or more. I always make the point to patients with milder acne that it is harder to make a more discernible difference. Do not be afraid to combine anti-inflammatory, anti-bacterial, anti-comedonal and anti-androgen treatments together if the clinical situation demands. The importance of compliance for successful treatment can never be overemphasised. However, many patients still require secondary referral due to inadequate response.

CRITERIA FOR REFERRAL

Present indications for referral for consideration for isotretinoin are:

REFERRAL GUIDELINES

- Have a severe variant such as acne fulminans (require urgent/same day referral), acne conglobata or gram-neg folliculitis
- Have severe or nodulocystic acne and could benefit from oral isotretinoin
- Have severe social/psychological problems including a morbid fear of deformity (dysmorphophobia) regardless of clinical severity of acne
- At risk of, or are developing, scarring/pigmentary disturbance despite primary care therapies
- Have moderate acne that has failed to respond to treatment which has included 2 courses of antibiotics, each lasting 12 weeks. Failure is probably best based on a subjective assessment by the patient
- Suspected of having an underlying problem in need of investigation
- Have, or develop, features that make the diagnosis uncertain

Many referrals for acne to secondary care remain inappropriate. It is clear to me from some referral letters that terms such as 'scarring' and 'severe' are often used misguidedly. In one research paper (albeit from 1989) in which consultant dermatologists were asked if they felt referrals from primary care were appropriate, overall 26% were considered not to be so; however, this rose to 38.7% in relation to acne.¹³

The mainstay of hospital treatment is isotretinoin; this is presently only available in secondary care, a few GPwER clinics and in the private sector. There is an ongoing debate whether this should be so. Historically, this has been the policy due to its perceived expense, its teratogenicity and, more latterly, due to concerns whether it is implicated in causing or worsening depression or even been implicated in suicide. There has been some intermittent media hype regarding the mental health concerns, but these are largely considered to be unfounded.¹⁴



BEFORE ROACCUTANE TREATMENT



AFTER 9 MONTHS TREATMENT



Isotretinoin is an incredibly potent and effective treatment for acne, producing a profound down regulation of the sebaceous gland activity. It has not been superseded in more than 30 years. It is the only dermatological drug which is truly a 'big player' in global pharmaceuticals. Although primary care physicians cannot prescribe isotretinoin as it is in common usage, they should know something of what their patients should expect.

Common side effects are cheilitis, which is almost invariable, dry skin, mild conjunctivitis and myalgia. More rarely, paronychia, hyperhidrosis, headaches and disordered liver function and lipid profile can occur.

Reliable contraception is absolutely necessary for at risk women for at least one month before starting treatment, during treatment and at least one month after finishing a course. A robust pregnancy prevention programme is required for all women of childbearing age. Sixty to seventy percent need only one course of treatment, although they may need ongoing conventional treatment thereafter. Prolonged courses or repeat courses may be required. A past history of mental illness, particularly depression, should be taken into account in the decision to prescribe but the evidence for any risk of self harm or suicide remains reassuringly low.¹⁴

TEACHING POINTS

- Each patient must be carefully assessed and a suitable treatment tailored to the individual within the broader framework of NICE guidance
- Any underlying psychosocial morbidity should be considered
- Be prepared to use combinations of treatment
- Patient compliance is a major influence in successful treatment

USEFUL SOURCES

BAD website: www.bad.org.uk

European guidelines: www.acne-guidelines.com

Acne vulgaris: management (nice.org.uk)

Acne vulgaris (pcds.org.uk)

Acne vulgaris (www.cks.nice.org.uk)

Acne - NHS (www.nhs.uk)

Patient support (www.acnesupport.org.uk)

Acne (www.dermnetnz.org)

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Contra-indications, warnings, side effects etc: Do not use if sensitive to any of the ingredients. Keep away from the eyes, inside the nostrils and mouth. Temporary tingling, itching or stinging may occur with emollients when applied to damaged skin. Such symptoms usually subside after a few days of treatment, however, if they are

troublesome or persist, stop using and seek medical advice. Rarely skin irritation (mild rashes) or allergic skin reactions can occur on extremely sensitive skin, these tend to occur during or soon after the first few uses and if this occurs stop treatment. Vitamin B derivative requirements are increased during pregnancy and infancy, however, with prolonged use over significant areas, it may be possible to exceed the minimum recommended levels of nicotinamide in pregnancy. Safety trials have not been conducted in pregnancy and breast feeding therefore, as with other treatments, caution should be exercised, particularly in the first three months of pregnancy.

Instruct patients not to smoke or go near naked flames. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a potential fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

Ingredients: Carbomer, glycerol, isopropyl myristate, liquid paraffin, nicotinamide, phenoxyethanol, sorbitan laurate, trolamine, purified water.



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Date of preparation: July 2020.

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