FREEDERM TREATMENT 4% W/W GEL
PL 00173/0398

UKPAR

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FREEDERM TREATMENT 4% W/W GEL
PL 00173/0398

LAY SUMMARY

The MHRA granted Diomed Developments Limited a Marketing Authorisation (licence) for the medicinal product Freederm Treatment 4% w/w Gel on 15th January 2009. This product, to be available to the general public (legal status "P"), contains nicotinamide. This ingredient treats pimples and spots by its anti-inflammatory activity, which reduces swelling, redness and tenderness. Nicotinamide is not an antibiotic, it is related to an essential vitamin in our diet (Vitamin B_3).

This application is a duplicate of a previously granted application for Nicam 4% w/w Gel, which was originally approved to Diomed Developments Limited on 10th September 2002 (PL 00173/0166).

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Freederm Treatment 4% w/w Gel outweigh the risks, hence a Marketing Authorisation has been granted.

FREEDERM TREATMENT 4% W/W GEL
PL 00173/0398

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Freederm Treatment 4% w/w Gel (PL 00173/0398) to Diomed Developments Limited on 15th January 2009. The product is available to the general public (legal status "P").

The application was submitted as a simple abridged application, according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Nicam 4% w/w Gel, which was originally approved to Diomed Developments Limited on 10th September 2002 (PL 00173/0166).

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.

The active ingredient is nicotinamide, an amide of nicotinic acid (vitamin B_3). This ingredient treats pimples and spots by its anti-inflammatory activity, which reduces swelling, redness and tenderness. The anti-inflammatory activity of nicotinamide is due to its suppression of antigen-induced lymphocytic transformation and inhibition of 3'-5' cyclic AMP phosphodiesterase. Nicotinamide has demonstrated the ability to block the inflammatory action of iodides, which are known to precipitate or exacerbate inflammatory acne.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 00173/0398
PROPRIETARY NAME: Freederm Treatment 4% w/w Gel
ACTIVE(S): Nicotinamide
COMPANY NAME: Diomed Developments Limited
E.C. ARTICLE: Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC
LEGAL STATUS: P

1. INTRODUCTION

This is a simple, piggy-back application for Freederm Treatment 4% w/w Gel, submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Diomed Developments Limited, trading as Dermal Laboratories, Tatmore Place, Gosmore, Hitchin, Hertfordshire SG4 7QR, United Kingdom.

The application cross-refers to Nicam 4% w/w Gel, which was originally approved to Diomed Developments Limited on 10th September 2002 (PL 00173/0166).

The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Freederm Treatment 4% w/w Gel. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains nicotinamide, equivalent to 4% w/w. The finished product is packaged in low-density polyethylene, low-density polyethylene/EVA copolymer tubes, with white polypropylene closures in pack sizes of 6, 25 and 60grams. The proposed shelf-life (24 months for the 6g and 25g packs, and 36 months for the 60g pack) and storage conditions (do not store above 25 degrees) are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the products will be available under the legal status “P” (i.e. available to the general public).

2.4 Marketing authorisation holder/Contact Persons/Company

Diomed Developments Limited, trading as Dermal Laboratories, Tatmore Place, Gosmore, Hitchin, Hertfordshire SG4 7QR, United Kingdom.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
No materials of animal or human origin are included in the product.

This information is consistent with the cross-reference product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the application are acceptable. The grant of a marketing authorisation is recommended.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data are consistent with those previously assessed for the cross-reference product and, as such, have been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

This application is identical to a previously granted application for Nicam 4% w/w Gel, which was originally approved to Diomed Developments Limited on 10th September 2002 (PL 00173/0166).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with nicotinamide is considered to have demonstrated the therapeutic value of the compound. The risk:benefit is, therefore, considered to be positive.

FREEDERM TREATMENT 4% W/W GEL
PL 00173/0398

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 05/03/2007.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 27/04/2007.
3	Following assessment of the application the MHRA requested further information on 03/09/2008.
4	The applicant responded to the MHRA's requests, providing further information on 03/11/2008.
5	The application was determined on 15/01/2009

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

FREEDERM TREATMENT 4% W/W GEL
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Freederm Treatment 4% w/w Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Nicotinamide 4% w/w
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Topical gel

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the topical treatment of mild to moderate inflammatory acne vulgaris.

4.2 Posology and method of administration
Apply to the affected area twice daily after the skin has been thoroughly washed with warm water and soap. Enough gel should be used to cover the affected area.

No difference in dose or dose schedule is recommended for adults, children or the elderly.

For topical administration only.

4.3 Contraindications
Contraindicated in persons who have shown hypersensitivity to any of its components.

4.4 Special warnings and precautions for use
For external use only and to be kept away from the eyes and mucous membranes, including those of the nose and mouth. If excessive dryness, irritation or peeling occurs reduce the dosage to one application per day or every other day.

4.5 Interaction with other medicinal products and other forms of interaction
None known.

4.6 Pregnancy and lactation
Vitamin B derivative requirements such as nicotinamide, are increased during pregnancy and infancy. Nicotinamide is excreted in breast milk. As with all medicines, care should be exercised during the first trimester of pregnancy.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects
The most frequently encountered adverse effect reported is dryness of the skin. Other less frequent adverse effects include pruritus, erythema, burning sensation and irritation.

4.9 Overdose
Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Niacin (nicotinic acid) is an essential B complex Vitamin (B3), whose deficiency results in the clinical syndrome known as pellagra. Nicotinic acid is converted in the body to nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP), which function as coenzymes for a wide variety of vital oxidation-reduction reactions. Nicotinamide (niacinamide), the active ingredient, is the physiologically active form of niacin and is the chemical form of Vitamin B3 found in virtually all multivitamin products. Though nicotinic acid and nicotinamide are so closely related chemically, they differ somewhat in pharmacological properties. Nicotinic acid products exhibit moderately intense cutaneous vasodilation, resulting frequently in mild headaches and flushing or tingling of the skin, but such reactions have not been observed with nicotinamide. Nicotinic acid has also been used for its effect to lower plasma cholesterol, again a property not shared by nicotinamide.

Nicotinamide has demonstrated beneficial effects on inflammatory acne. It is considered that these effects are related to its significant anti-inflammatory activity.

5.2 Pharmacokinetic properties

Following oral administration, nicotinamide is readily absorbed from the gastro- intestinal tract and widely distributed in the body tissues. The main route of metabolism is the conversion to N - methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinuric acid is also formed. Small amounts of nicotinamide are excreted unchanged in the urine; this amount increases with larger doses.

5.3 Preclinical safety data

Nicotinic acid amide (nicotinamide) has been recognised since 1937 as an essential B complex vitamin whose deficiency results in the clinical syndrome known as pellagra. It is widely available, in tablets and in sterile solution in water for intravenous administration, for the prophylaxis and treatment of pellagra and nutritional deficiency.

In the United States, nicotinamide is included in the Food and Drug Administration's listing of nutritional agents which are Generally Recognised As Safe (GRAS).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium magnesium silicate
Hypromellose
Citric acid anhydrous
Macrogol lauryl ether
Ethanol anhydrous
Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months - for 60 g pack.
24 months - for 6 g and 25 g packs

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Low density polyethylene or co-extruded low density polyethylene laminate 60g, 25 g and 6g tube with white polypropylene cap.

6.6 Special precautions for disposal

None stated

7 MARKETING AUTHORISATION HOLDER

Diomed Developments Limited
trading as Dermal Laboratories
Tatmore Place
Gosmore
Hitchin
Hertfordshire SG4 7QR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00173/0398

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/01/2009

10 DATE OF REVISION OF THE TEXT

15/01/2009

PACKAGE LEAFLET Information for the user

Freederm®

Nicotinamide treatment 4% w/w gel

Please read all of this leaflet carefully before using this product.
Keep this leaflet. You may need to read it again.
Ask your doctor or pharmacist if you need more information or advice.

In this leaflet:

1. WHAT FREEDERM TREATMENT GEL IS AND WHAT IT IS USED FOR

- Freederm Treatment Gel is a skin treatment for inflamed pimples and spots.
- The medical term for this condition is mild to moderate inflammatory acne vulgaris. It involves inflamed pimples (papules) and spots containing pus (pustules), often with skin redness (erythema) and some tenderness. The condition occurs mainly on the face, back and chest.
- Freederm Treatment Gel is suitable for use by **adults, children and the elderly.**
- The **active ingredient** in this product is nicotinamide. This ingredient treats pimples and spots by its anti-inflammatory activity, which reduces swelling, redness and tenderness.
- Nicotinamide is not an antibiotic, it is related to an essential vitamin in our diet (Vitamin B_3).

2. BEFORE YOU USE FREEDERM TREATMENT GEL

Do not use Freederm Treatment Gel if you are **allergic (hypersensitive)** to nicotinamide or any of the other ingredients of Freederm Treatment Gel listed in Section 6.

Take care when using this product:

- Only apply it to your skin.
- When using it on your face, keep it away from your eyes, and avoid getting it inside your nostrils, on your lips or inside your mouth.
- Depending on how sensitive your skin tends to be, it may be a good idea initially to test the gel on a small area, and wait 24 hours before using it on larger areas. This is especially advisable if you have unusually sensitive skin or if you are treating the face (as generally applies when using any new treatment for the first time).

Using other medicines
Freederm Treatment Gel is not known to affect, or to be affected by, any other medicines.

Pregnancy and breast-feeding
There are no specific restrictions to using Freederm Treatment Gel during pregnancy or breast-feeding. Vitamin B derivative requirements, such as nicotinamide, are increased during pregnancy and infancy. However, although there are no known potential risks, as with any medicine caution should be exercised, particularly in the first three months of pregnancy. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machinery
Using this product is not known to affect your ability to drive or use machinery.

3. HOW TO USE FREEDERM TREATMENT GEL

For adults, children and the elderly:
Apply the gel **twice daily** over and around the affected skin areas as follows:

- Wash the area.
- Gently pat the skin dry (avoid rubbing as this may aggravate the skin).
- Apply a thin film of gel, and gently massage it in.

Continue using the gel twice daily in this way for as long as necessary, (unless irritation occurs - see Section 4). Depending on the severity of your acne, it can take several weeks for the skin's normal repair process to work before you see a real improvement in your skin.

If the product gets into the eyes or mouth
The product may cause irritation if it gets into the eyes or mouth. Rinse affected areas with plenty of water. If rinsing one eye, take care to avoid washing product into the other eye. If irritation persists tell your doctor or pharmacist.

If you forget to use this product
Do not worry if you occasionally forget to use this product, just carry on using it when you remember.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Although Freederm Treatment Gel has been specially designed for use on all skin types including problem skin, it can cause side effects, although not everybody gets them.

- Occasionally, susceptible individuals can experience local skin dryness. If this is unacceptable, or causes irritation or peeling, try applying the gel only once a day or every other day.
- Very occasionally, **allergic** reactions such as itching (pruritus), redness (erythema), swelling or burning sensations can occur.

Stop using this product and **tell** your doctor or pharmacist if any side effect gets serious, or you notice any other side effects not mentioned in this leaflet.

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5. HOW TO STORE FREEDERM TREATMENT GEL

- Keep it out of the reach and sight of children.
- Always replace the cap tightly after use.
- Do not store the product above 25°C.
- Do not use after the expiry date shown on the tube and carton. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION ABOUT FREEDERM TREATMENT GEL

What Freederm Treatment Gel contains:

The **active ingredient** is **nicotinamide** (4% w/w).

The **other ingredients** are aluminium magnesium silicate, hypromellose, citric acid anhydrous, macrogol lauryl ether, ethanol anhydrous and purified water.

What Freederm Treatment Gel looks like and contents of the pack

- The product is a translucent gel.
- The product is available in tubes containing 25g of gel.

The Marketing Authorisation holder is Diomed Developments Ltd, Tatmore Place, Gosmore, Hitchin, Hertfordshire, SG4 7QR, UK.

The Manufacturer is Pharmasol Ltd, North Way, Walworth Industrial Estate, Andover, Hampshire, SP10 5AZ, UK.

This leaflet was last approved in January 2009.

HEALTH EDUCATION INFORMATION

What is Acne?

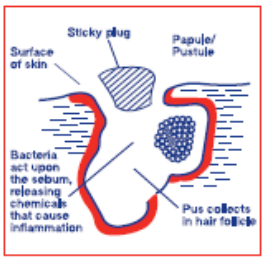
Acne is a skin disorder that occurs mainly on the face, back and chest. It affects a high proportion of both sexes, most commonly between the ages of 14 and 20, although it can last well into adulthood or even occur for the first time in adults. The early stages of acne often involve blackheads and whiteheads (doctors refer to these as 'comedones'). These can develop into red or inflamed pimples or spots ('papules') which often contain pus (so-called 'pustules'). In a few severe cases, groups of spots may become very inflamed and form cysts. Acne is a very common skin complaint, affecting about 70% of teenagers. Whether you have just a few spots, or a hundred, it tends to be regarded as acne.

What Causes Acne?

Acne is not caused by eating too many sweets, chocolate or fatty foods (although healthy eating and a healthy lifestyle is good for your general health). Neither is it caused by not washing properly (although a good skin care routine is an important part of treatment). The exact cause of acne is not fully understood, but we do know that it involves the hair follicles in our skin and their associated oil-producing glands (the so-called "pilosebaceous units"). Often around the onset of puberty, hormones stimulate increased production of sebum (oil) by these glands. Although normally this sebum flows out to lubricate the skin, when too much of it is produced it can become trapped within the pilosebaceous units where it forms a dark coloured plug or 'blackhead' where the opening is wide, or a light coloured plug or 'whitehead' where the opening is narrow. Inflammatory acne begins when a common type of skin bacteria called P. acnes – which is normally harmless – starts to break down the trapped sebum. This process releases chemicals that cause inflammation in the surrounding skin, and leads to redness and the formation of 'angry' or inflamed-looking pimples and spots. These feel sore and tender, frequently contain pus and eventually burst open onto the skin before settling down. If the inflammation is deep in the hair duct, or if the spot is squeezed too early or aggressively, the pus can rupture into the skin and cause even more inflammation, and in extreme cases can even cause scarring.

Important tips when treating acne

- Take care to cleanse your skin thoroughly and regularly, but try not to clean too aggressively as this can make matters worse.
- Many acne patients find their skin becomes excessively dry. If this happens, ask your doctor or a pharmacist about suitable skin moisturisers.
- Carefully follow the instructions supplied with any medication you are using, as this will give you the best chance of clearing your condition.
- When using treatments applied to the skin, you will need to treat all the involved skin area, not just each individual spot.
- Try to avoid picking or severely squeezing your spots because this can make matters worse and lead to scarring.
- Persevere with treatment because it can take several weeks for the skin's normal repair process to work.
- For further independent help and advice, contact the Acne Support Group www.stopspots.org.



To listen to or request a copy of this leaflet in Braille, large print or audio, please call free of charge: 0800 198 5000 (UK only).

Please be ready to give the following information:
Freederm Treatment Gel, 00173/0398.

This is a service provided by the Royal National Institute of Blind People (RNIB).

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FREEDERM TREATMENT 4% W/W GEL
PL 00173/0398
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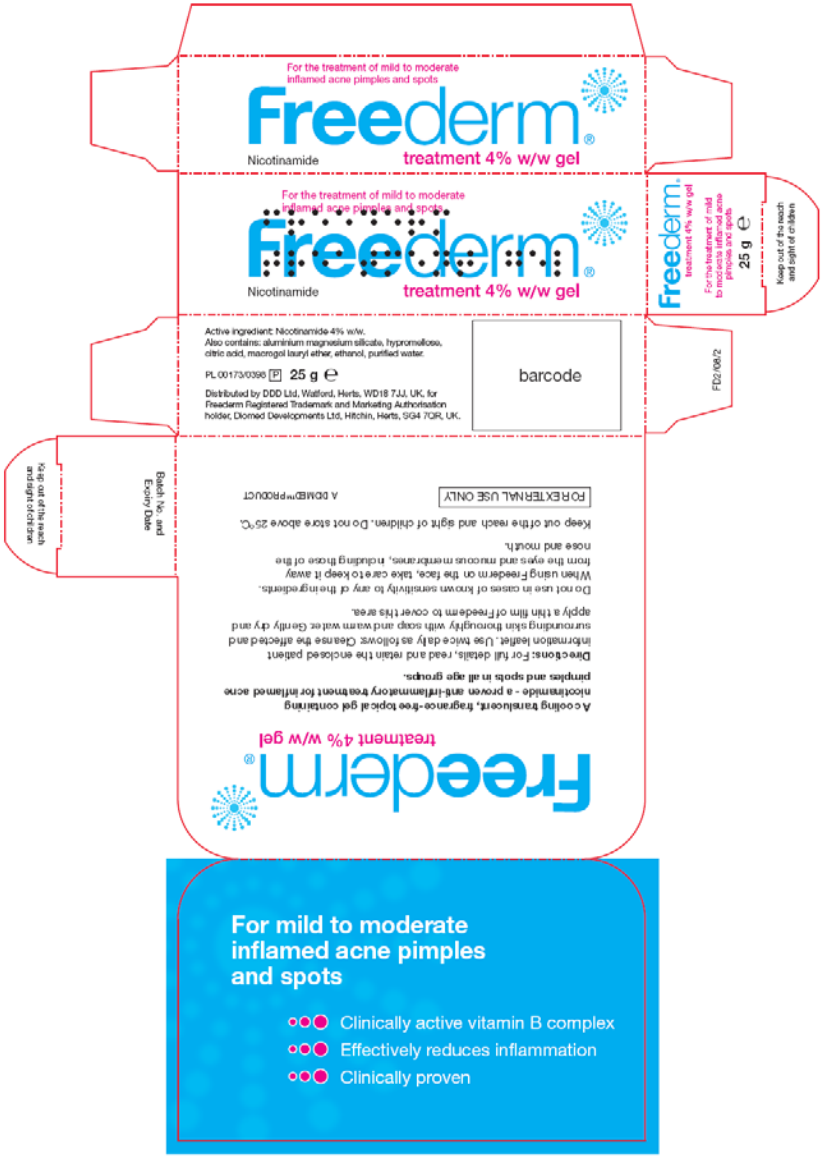

For the treatment of mild to moderate inflamed acne pimples and spots

Freederm®

Nicotinamide treatment 4% w/w gel

Directions: For full details, read and retain the accompanying patient information leaflet. Use twice daily as follows: Cleanse the affected and surrounding skin thoroughly with soap and warm water. Gently dry and apply a thin film of Freederm to cover this area. Keep out of the reach and sight of children. Do not store above 25°C.

Active ingredient: Nicotinamide 4% w/w. Also contains: aluminium magnesium silicate, hypromellose, citric acid, macrogol lauryl ether, ethanol, purified water.

PL 00173/0398 P 25 g e FOR EXTERNAL USE ONLY

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Batch No. & Expiry Date on crimp.

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