CONFIDENTIAL

ACNM
ITEM No:
MEETING: In-house

ZO-RUB (previously ZACIN) HP TOPICAL ANALGESIC CREAM 0.075% capsaicin tube

ZO-RUB (previously ZACIN) OA TOPICAL ANALGESIC CREAM 0.025% capsaicin tube

Second Supplementary Report

Sponsor: AFT Pharmaceuticals
Sub ID: OM-2009-00970-3 &OM-2009-00969-3
TGA file: 2009/009230 & 2009/009229
Prepared by: s22
Date: May 2012

Active Ingredients	HP Quantity	OA Quantity	Role in formulation*	Specification
Capsaicin	0.075% w/w	0.025% w/w	Active	USP/NF
Excipients				
Benzyl alcohol	s47% w/w	s47% w/w	Preservative	BP
Sorbitol solution 70% non-crystallising	s47% w/w	s47% w/w	Humectant	BP
Isopropyl myristate	s47% w/w	s47% w/w	Emollient	BP
Cetyl alcohol	s47% w/w	s47% w/w	Thickener	BP
Paraffin – soft white	s47% w/w	s47% w/w	Emollient	BP
Water – purified	s47% w/w	s47% w/w	Diluent	USP/NF
Proprietary Ingredient				
Cithrol GMS A/s (PI. No 2147)	s47% w/w	s47% w/w	Emulsifyer	C

*As stated by sponsor

Sponsor's amended indications for 0.075% capsaicin cream:

1. For the symptomatic relief of neuralgia associated with the following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed.
2. For the symptomatic management of medically diagnosed painful diabetic peripheral polyneuropathy.

Sponsor's proposed indications for 0.025% capsaicin cream:

For the symptomatic relief of pain associated with osteoarthritis.

Requested shelf life:
36 months when stored below 30°C

Poisons schedule:
Not scheduled

Attachments to evaluation report:

1. Labels

2. Consumer Medicine Information/Package insert

ZO-RUB (previously ZACIN) HP TOPICAL ANALGESIC CREAM 0.075% capsaicin tube

ZO-RUB (previously ZACIN) OA TOPICAL ANALGESIC CREAM 0.025% capsaicin tube

Second Supplementary Report

Issues

1. **Change to proprietary ingredient source of PEG-100 stearate and glyceryl monostearate proposed.**

These are **NEW PRODUCT** applications.

Background

The proposed 0.075% capsaicin cream is indicated for symptomatic relief of post-herpetic neuralgia and diabetic polyneuropathy. One other 0.075% capsaicin cream (Zostrix HP Cream, AUST R 10344) is included on the ARTG. This product was grandfathered and has the indications "*A topical analgesic cream for the management of medically diagnosed painful diabetic neuropathy or postherpetic neuralgia*".

The proposed 0.025% capsaicin cream is indicated for symptomatic relief of the pain of osteoarthritis. One other 0.025% capsaicin cream (Zostrix Cream, AUST R 19658) is included on the ARTG. This product was grandfathered and has the indications "*May be useful as an adjunct in the temporary relief of pain associated with arthritis. May be useful for the treatment of post-herpetic neuralgia (pain following shingles)*".

The indications for the two Zostrix Creams currently on the ARTG have not been fully evaluated.

These applications were originally evaluated in May and June 2011, and a letter dated 10 June 2011 sent to the sponsor raising issues to be addressed. The sponsor replied to those issues in correspondence dated 2 September. The sponsor's response was evaluated in October 2011, and a letter dated 14 October 2011raising further issues to be addressed was sent to the sponsor. The sponsor responded to these further issues in correspondence dated 14 March 2012. The sponsor's latestresponses are evaluated below (question to sponsor in bold font, summary and evaluation of responses in normal font).

Product Name

1. **You have proposed the names "Maxi-Rub Osteo Pain Relief" for the 0.025% capsaicin cream, and "Maxi-Rub Neuropathic Pain Relief" for the 0.075% capsaicin cream.**

The term "Maxi" in the proposed names will clearly be understood by consumers as short for "maximum". The term "maximum" (and shortened variations) has only been allowed in product names that clearly represent the maximum strength or maximum dose of the active ingredient. Therefore while the name "Maxi-Rub" may be acceptable for the higher strength cream (previously Zacin HP), it is not acceptable for the lower strength cream (previously Zacin OA). Further, the terms "Osteo" and "Neuropathic" in the product names, do not clearly differentiate the two products as two different strengths, and it is possible that consumers could assume that the two products are the same, but with new packaging. Finally, the term "Neuropathic Pain" is not acceptable for the higher strength product since there are many different sorts of neuropathic pain, and the product is not indicated for all or most of these. In addition "Neuropathic Pain" is not likely to be a term understood by a majority of consumers.

For the above reasons, the proposed names Maxi-Rub Osteo Pain Relief and Maxi-Rub Neuropathic Pain Relief are considered unacceptable, and you are requested to propose new names for the products.

The sponsor now proposes the names Zo-Rub OA and Zo-Rub HP for the two products. There are no objections to these proposed names.

Clinical data

2. **You have stated that the formulations of the proposed products are** s47 [redacted]

If the formulation of the proposed products is s47 [redacted] **Therefore please provide confirmation of the statement that the** s47 [redacted] **Otherwise, justification for the relevance of the provided clinical studies to the proposed formulations would be required, as previously requested (Qn 2 of correspondence dated 6 June 2011).**

The sponsor argues that the proposed products are s47 [redacted]

The sponsor supports the fact that s47 [redacted] with the following data:

- A statement that the trade names s47 [redacted]

- A letter dated 24 November 2000 from Bioglan Laboratories stating that they s47 the product name. AFT Pharmaceuticals is the sponsor of Zostrix in New Zealand, and confirms that s47

- A Therapeutic Products Database entry from Medsafe NZ showing the quantitative formulation of Zostrix HP and Zostrix OA, s47

In addition to the information provided by the sponsor, the formulations of the proposed products have been compared to the formulations of Zostrix creams as registered on the ARTG (comparison of the HP variants below).

Formulation comparison of Zacin HP Cream and Zostrix HP Cream

Ingredient	Zacin HP	Zostrix HP
Capsaicin	0.075% w/w	0.075% w/w
Benzyl alcohol	s47% w/w	s47% w/w
Sorbitol solution 70% non-crystallising	s47% w/w	s47% w/w
Isopropyl myristate	s47% w/w	s47% w/w
Cetyl alcohol	s47% w/w	s47% w/w
Paraffin – soft white	s47% w/w	s47% w/w
glyceryl monostearate/PEG-100 stearate	s47% w/w[1]	s47% w/w[1]
Water - purified	s47% w/w	s47% w/w

1. The glyceryl monostearate/PEG-100 stearate mix in Zacin is currently s47 (although see under starting material specifications below) while in Zostrix it is s47 The quantitative composition of the two proprietary ingredients is not known.

The data provided by the sponsor, and supported by information from the ARTG, is considered s47 The different proprietary ingredient sources of glyceryl monostearate and PEG-100 stearate are not considered to be significant enough to create a clinically meaningful difference in the efficacy of the products even if the efficacy is formulation dependent. Therefore the clinical data provided with the original application is considered relevant to the proposed products.

Labelling - Zacin HP

3. The directions for use should be amended to include the patient population (Adults).

The label has been amended as requested.

[1] The formulation on the NZ database lists the products as containing s47% glyceryl stearate instead of s47% glyceryl monostearate/PEG-100 stearate mix. However, this is the s47

CMI/pack insert – Zacin HP

4. There is still a discrepancy between the frequency of use in the CMI (4 times per day) and on the product label (3-4 times per day). Please amend the frequency of use in the CMI to "3-4 times per day" to be consistent with the product label.

The CMI has been amended as requested.

Starting material specifications

5. It is noted that you have confirmed that the PEG-100 Stearate complies with the relevant Ph. Eur monograph, but that the glyceryl monostearate does not comply with a compendial monograph. While the raw material specification for the proprietary ingredient contains some of the tests included in the BP and USP/NF monographs for glyceryl monostearate, it does not control the impurities that are controlled by the monographs (heavy metals, free glycerol). Please either ensure that the glycerol monostearate raw material used in the proprietary ingredient complies with compendial monographs, or amend the raw material specification for the proprietary ingredient to include suitable controls over heavy metals and free glycerol.

The sponsor proposes to change the proprietary ingredient that is the source of the PEG-100 stearate and glyceryl monostearate from s47 [redacted] to s47 [redacted] The sponsor asserts that the only difference between the two proprietary ingredients is the grade of the starting materials, and in s47 [redacted] both starting materials comply with the relevant compendial monographs. s47 [redacted] s47, manufactured by s47 [redacted] does not appear to be registered as a proprietary ingredient in Australia. The sponsor will be advised that if s47 [redacted] s47 is registered as a proprietary ingredient in Australia, the sponsor should provide the registered proprietary ingredient number. Alternatively, if they know the actual ratios of PEG-100 stearate and glyceryl monostearate in the ingredient, they should provide that information to the TGA. If this information is confidential to the finished product sponsor, an application for proprietary ingredient status for s47 [redacted] must be submitted by the manufacturer of the proprietary ingredient.

The significance of this change to the source of the PEG-100 stearate and glyceryl stearate in terms of whether the formulations of the proposed products are s47 [redacted]

Stability data

6. The updated stability data support a shelf life of 24 months when stored below 30°C for both product strengths.

The sponsor argues that the stability data provided to date (24 months real time and 6 months accelerated) supports a shelf life of 26 months based on the ICH guideline Q1E. However, the OTC section does not accept extrapolation of the real time data by 12 months to allocate a shelf life, as recommended by the ICH Guideline. Therefore, a shelf life

of 24 months when stored below 30°C should be allocated for both products, as previously advised to the sponsor.

Pee reviewed 6/10
83

Document 2

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ACNM
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ZACIN HP TOPICAL ANALGESIC CREAM 0.075% capsaicin tube

ZACIN OA TOPICAL ANALGESIC CREAM 0.025% capsaicin tube

Supplementary Report

Sponsor: AFT Pharmaceuticals
Sub ID: OM-2009-00970-3 &OM-2009-00969-3
TGA file: 2009/009230 & 2009/009229
Prepared by: s22
Date: October 2011

Active Ingredients	HP Quantity	OA Quantity	Role in formulation*	Specification
Capsaicin	0.075% w/w	0.025% w/w	Active	USP/NF
Excipients				
Benzyl alcohol	s47% w/w	s47% w/w	Preservative	BP
Sorbitol solution 70% non-crystallising	s47% w/w	s47% w/w	Humectant	BP
Isopropyl myristate	s47% w/w	s47% w/w	Emollient	BP
Cetyl alcohol	s47% w/w	s47% w/w	Thickener	BP
Paraffin – soft white	s47% w/w	s47% w/w	Emollient	BP
Glyceryl monostearate – self emulsifying	s47% w/w	s47% w/w	Emulsifier	C
Water - purified			Diluent	USP/NF

*As stated by sponsor

Sponsor's proposed indications for 0.075% capsaicin cream:

1. For the symptomatic relief of neuralgia associated with the following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed.
2. For the symptomatic management of painful diabetic peripheral polyneuropathy.

Sponsor's proposed indications for 0.025% capsaicin cream:

For the symptomatic relief of pain associated with osteoarthritis.

Requested shelf life:
36 months when stored below 30°C

Poisons schedule:
Not scheduled

Attachments to evaluation report:

1. Labels
2. Consumer Medicine Information/Package insert

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ZACIN HP TOPICAL ANALGESIC CREAM 0.075% capsaicin tube

ZACIN OA TOPICAL ANALGESIC CREAM 0.025% capsaicin tube

Supplementary Report

Issues

1. **Support for lack of formulation dependence required.**
2. **Revised product name still unacceptable.**
3. **Further minor amendments to label and CMI/pack insert required.**
4. **Amendment to starting material specifications for proprietary ingredient required.**
5. **Stability data supports shelf life of 2 years when stored below 30°C**

These are **NEW PRODUCT** applications.

Background

The proposed 0.075% capsaicin cream is indicated for symptomatic relief of post-herpetic neuralgia and diabetic polyneuropathy. One other 0.075% capsaicin cream (Zostrix HP Cream, AUST R 10344) is included on the ARTG. This product was grandfathered and has the indications "*A topical analgesic cream for the management of medically diagnosed painful diabetic neuropathy or postherpetic neuralgia*".

The proposed 0.025% capsaicin cream is indicated for symptomatic relief of the pain of osteoarthritis. One other 0.025% capsaicin cream (Zostrix Cream, AUST R 19658) is included on the ARTG. This product was grandfathered and has the indications "*May be useful as an adjunct in the temporary relief of pain associated with arthritis. May be useful for the treatment of post-herpetic neuralgia (pain following shingles)*".

The indications for the two Zostrix Creams currently on the ARTG have not been fully evaluated.

These applications were originally evaluated in May and June 2011, and a letter dated 10 June 2011 sent to the sponsor raising issues to be addressed. The sponsor has replied to these issues in correspondence dated 2 September. The sponsor's responses are evaluated below (question to sponsor in bold font, summary and evaluation of responses in normal font).

Product Name

1. **"Zacin" is very similar to "Zactin", which is the trade name of a range of fluoxetine tablets indicated for the treatment of depression. The different dose forms, indications and schedules of Zacin and Zactin, may make it unlikely that consumers would confuse Zacin and Zactin**

at the point of use. However, the two names are considered both look-alike and sound alike names, and could be confused at other points in the chain between manufacture and product use, including by health professionals. Therefore the proposed product names "Zacin HP" and "Zacin OA" are considered unacceptable. Please propose alternative names for the two products. Amended labels and CMI/pack insert including the new product names should also be provided.

The sponsor proposes to use the name Maxi-Rub Osteo Pain Relief for Zacin OA, and Maxi-Rub Neuropathic Pain Relief for Zacin HP.

The term "Maxi" in the proposed names will clearly be understood by consumers as short for "maximum". The term "maximum" and shortened variations has only been allowed in product names that clearly represent the maximum strength or maximum dose of the active ingredient. Therefore while the name "Maxi-Rub" may be acceptable for the higher strength cream (previously Zacin HP), it is not acceptable for the lower strength cream (previously Zacin OA). Further, the terms "Osteo" and "Neuropathic" in the product names, do not clearly differentiate the two products as two different strengths, and it is possible that consumers could assume that the two products are the same, but with new packaging. Finally, the term "Neuropathic Pain" is not acceptable for the higher strength product since there are many different sorts of neuropathic pain, and the product is not indicated for all or most of these. In addition "Neuropathic Pain" is not likely to be a term understood by a majority of consumers.

For the above reasons, the sponsor's proposed names Maxi-Rub Osteo Pain Relief and Maxi-Rub Neuropathic Pain Relief are considered unacceptable, and the sponsor will be requested to propose new names for the products.

..Clinical data

2. You are advised that the TGA has concerns over whether the efficacy and safety of capsaicin topical products are formulation dependent. Please justify the relevance of the submitted clinical studies to the proposed products, with reference to the possibility of the formulation dependency of efficacy and safety.

The sponsor has indicated that the formulations of the proposed products are s47 [redacted] However, the references provided by the sponsor did not all use s47 [redacted] as the test article – some studies used s47 [redacted] while others used s47 [redacted] capsaicin cream, whose formulation is not stated, and the majority did not name the brand or describe the formulation of the capsaicin cream. It is unclear whether the sponsor is indicating in their response that all 0.025% and 0.075% capsacin creams have the same formulation.

If the formulation of the proposed products is s47 [redacted] creams, the issue of formulation dependence becomes irrelevant because the s47 [redacted] Therefore the sponsor will be requested to provide

confirmation of the statement that the formulations of the proposed products are s47 [redacted] This confirmation could be in the form of physico-chemical testing demonstrating that the formulations are s47 [redacted] to use the formulation.

ARTG indications – Zacin HP

3. **The ARTG indications for Zacin HP should be revised to *"1. For the symptomatic relief of neuralgia following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed. 2. For the symptomatic management of medically diagnosed painful diabetic peripheral polyneuropathy"* to correct grammatical errors and to ensure consistency with the proposed label indications.**

The sponsor has agreed to the suggested change in the wording of the ARTG indications.

Labelling - Zacin HP

4. **As indicated above, the directions for use on the tube and carton label should be amended to include *"For further information on how to use this product see the pack insert"* or similar.**

5. **The recommended patient population of "adults and children over 2 years of age" is not consistent with the subjects used in the clinical studies, nor with the pack statement *"Not recommended for use on children"*. The recommended patient population should be amended to *"Adults"*.**

6. **The storage instruction on the label is "Store below 25°C" but the requested storage instruction in the application form is "Store below 30°C". The real time stability studies were conducted at 30°C, and therefore the label should be amended.**

7. **The presence of the preservative, benzyl alcohol, should be declared on the tube and carton labels.**

The sponsor has made the requested changes to the product labels, except that the directions for use now do not refer to the intended patient population (Adults). The directions for use should be amended to include the patient population (Adults).

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Labelling - Zacin OA

8. **As indicated above, the directions for use on the tube and carton label should be amended to include "*For further information on how to use this product see the pack insert*" or similar.**

9. **The storage instruction on the label is "Store below 25°C" but the requested storage instruction in the application form is "Store below 30°C". The real time stability studies were conducted at 30°C, and therefore the label should be amended.**

10. **The presence of the preservative, benzyl alcohol, should be declared on the tube and carton labels.**

The sponsor has made the requested changes to the product labels.

CMI/pack insert – Zacin HP

11. **Under "What is in this leaflet", "It summaries..." should be amended to "It summarises.."**

12. **Under "What Zacin HP is used for and how it works" the concentration of capsaicin should be amended to 0.075%.**

13. **Under "How to use Zacin HP" the reference to "Zaxon" should be amended to "Zacin".**

14. **The frequency of use of the product should be consistent between the product label and the CMI. Therefore either both should refer to use 3-4 times daily, or both should refer to use 4 times daily.**

15. **References in the CMI to rubbing into the affected joint should be amended to refer to rubbing into the affected area, since not all cases of diabetic neuropathy or post-herpetic neuralgia are in joints. The reference to the amount of product to use should also be amended so that it does not refer only to joints, as should the reference to arthritic hand joints (in the section about washing residue off hands).**

16. **Although the CMI contains references to not using the product on broken skin, given that the product is intended for use after an episode of shingles, it should be recommended to the sponsor that the CMI include a specific reference to not using the product for pain after shingles until the open shingles lesions have healed.**

17. **The storage condition should be amended to "Store below 30°C" consistent with the stability data.**

18. **The reference to not using tight bandages over the cream should be moved from the Storage section of the CMI to under "Things you must not do".**

19. **A reference to coughing (as noted in the clinical studies) should be included in the "Side Effects" section of the CMI and also under "How to use it" (as with reference to the burning sensation). If the sponsor wishes, a statement indicating that coughing may be minimised if the cream is not allowed to dry on the skin (or similar) could be included.**

20. **The instruction "Do not stop using Zacin HP, or lower the dosage, without checking with your doctor" is not necessary and not appropriate for a topical analgesic, even one that may take several weeks to produce an effect. The statement should be removed. If the sponsor wishes, it could be replaced with a statement to the effect that pain may return if treatment is stopped, or similar.**

21. **Under Product Description, the sponsor should include a description of the cream and the pack sizes available (for instance, Zacin HP is a viscous white cream which is available in 25 g and 45 g tubes).**

The sponsor has made the requested changes to the CMI. However, there is still a discrepancy between the frequency of use in the CMI (4 times per day) and on the product label (3-4 times per day). The sponsor should be requested to amend the frequency of use in the CMI to "3-4 times per day" to be consistent with the product label.

CMI/pack insert – Zacin HP

22. **Under "What is in this leaflet", "It summaries..." should be amended to "It summarises.."**

23. **The storage condition should be amended to "Store below 30°C" consistent with the stability data.**

24. **The reference to not using tight bandages over the cream should be moved from the Storage section of the CMI to under "Things you must not do".**

25. **The instruction "Do not stop using Zacin OA, or lower the dosage, without checking with your doctor" is not necessary and not appropriate for a topical analgesic, even one that may take several weeks to produce an effect. The statement should be removed. If the sponsor wishes, it could be replaced with a statement to the effect that pain may return if treatment is stopped, or similar.**

26. **The frequency of use of the product should be consistent between the product label and the CMI. Therefore either both should refer to use 3-4 times daily, or both should refer to use 4 times daily.**

27. **Under "How to use Zacin OA" the reference to "Zaxon" should be amended to "Zacin".**

28. **Under Product Description, the sponsor should include a description of the cream and the pack sizes available (for instance, Zacin OA is a viscous white cream which is available in 25 g and 45 g tubes).**

The sponsor has made the requested changes to the CMI.

Manufacturing

29. **The GMP Clearance certificate provided for the finished product manufacturer, s47 [redacted] expired in November 2010. Please provide a current GMP Clearance certificate for this manufacturer.**

An updated GMP Clearance has been provided. This is satisfactory.

30. **Process validation data for three production bulk batches of each product has been provided. Consistent with usual practice, please provide a written assurance that the manufacturing process validation for both proiducts has been conducted according to the requirements of the Code of Good Manufacturing Practice (the *Therapeutic Goods (Manufacturing Principles) Determination No. 1 2009* contains a definition of 'the Code').**

The sponsor has provided the requested assurance. This is satisfactory.

Starting material specifications

31. **The application forms list glyceryl monostearate as an ingredient in the creams at a concentration of s47 [redacted]% w/w. However, the pharmaceutical development section of the dossiers indicate that the emulsifier in the products is actually a mixture of glyceryl monostearate and PEG-100 stearate. It appears that this mixture is purchased as s47 [redacted] This ingredient is included on the ARTG with proprietary ingredient number s47 [redacted] The ratio of glyceryl monostearate and PEG-100 stearate in the mixture is not stated. Please confirm that the emulsifier in the products is actually s47 [redacted] and not glyceryl monostearate.**

The sponsor has confirmed that the ingredient used in the product is actually s47 [redacted] The application form should be amended administratively.

32. **If the emulsifier is a mixture of glyceryl monostearate and PEG-100 stearate, please provide an assurance that the glyceryl monostearate and PEG-100 stearate from which the mixture is composed comply with compendial monographs. Also, please show that the raw material specification for the mixture is capable of differentiating between different ratios of glyceryl monostearate and PEG-100 stearate.**

The sponsor has confirmed that the PEG-100 Stearate complies with the relevant Ph. Eur monograph. The glyceryl monostearate does not comply with a compendial monograph. While the raw material specification for the proprietary ingredient contains some of the tests included in the BP and USP/NF monographs for glyceryl monostearate, it does not control the impurities that are controlled by the monographs (heavy metals, free glycerol). The sponsor should either ensure that the glycerol monostearate raw material used in the proprietary ingredient complies with compendial monographs, or amend the raw material specification for the proprietary ingredient to include suitable controls over heavy metals and free glycerol.

The sponsor asserts that the saponification test and limits control the ratio of glyceryl monostearate and PEG-100 stearate in the proprietary ingredient. This is acceptable.

Finished product specifications

33. **Please amend the microbial limits in the finished product specifications for both products to be consistent with TGO 77.**

The sponsor has amended the microbial limits as requested. This is acceptable.

Test methods and analytical validation

Assay of capsaicin and capsaicinoids

34. **Please provide the limit of quantitation for the assay of capsaicinoids, and not just the limit of detection. Calculations and results used to determine the LOQ should also be provided. You are reminded that the LOQ of the assay should be considered in terms of the capsaicinoid limits in the finished product specifications, to ensure that the assay is capable of detecting changes in the capsaicinoid content.**

The sponsor has provided a revised validation for the assay of capsaicinoids. The revised validation is acceptable, and demonstrates that the LOQ and LOD of the assay (based on signal to noise ratio) are s47 mg/mL and s47 mg/mL capsaicinoids respectively. Although the LOQ and LOD are expressed in mg/mL and the limits for capsaicinoids are expressed in %w/w, it appears that the assay is capable of detecting changes in the capsaicinoid content.

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Stability data – Zacin HP

35. **To date only 6 months real time and 6 months accelerated stability data have been provided. These data are insufficient to support the requested shelf life of 36 months when stored below 30°C, and currently only support a shelf life of 12 months at this storage temperature. Based on the starting dates of the stability studies, at least 24 months real time stability data should be available by now. Please submit this additional stability data to support the requested shelf life.**

The sponsor has provided updated stability data. Stability data on three production-sized batches of product stored for 6 months at 40°C/75%RH and 24 months at 30°C/75%RH have been provided. These data demonstrate satisfactory stability of the product for up to 24 months at 30°C and support a shelf life of 24 months when stored below 30°C.

Stability data – Zacin OA

36. **To date only 6 months real time and 6 months accelerated stability data have been provided. These data are insufficient to support the requested shelf life of 36 months when stored below 30°C, and currently only support a shelf life of 12 months at this storage temperature. Based on the starting dates of the stability studies, at least 18 months real time stability data should be available by now. Please submit this additional stability data to support the requested shelf life.**

The sponsor has provided the updated stability data. Stability data on three production-sized batches of product stored for 6 months at 40°C/75%RH and 24 months at 30°C/75%RH have been provided. These data demonstrate satisfactory stability of the product for up to 24 months at 30°C and support a shelf life of 24 months when stored below 30°C.

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ZACIN HP TOPICAL ANALGESIC CREAM 0.075% capsaicin tube

Sponsor: AFT Pharmaceuticals
Sub ID: OM-2009-00969-3
TGA file: 2009/009229
Prepared by: s22
Date: June 2011

Active Ingredients	Quantity	Role in formulation*	Specification
Capsaicin	0.075% w/w	Active	USP/NF
Excipients			
Benzyl alcohol	s47% w/w	Preservative	BP
Sorbitol solution 70% non-crystallising	s47% w/w	Humectant	BP
Isopropyl myristate	s47% w/w	Emollient	BP
Cetyl alcohol	s47% w/w	Thickener	BP
Paraffin – soft white	s47% w/w	Emollient	BP
Glyceryl monostearate – self emulsifying	s47% w/w	Emulsifier	C
Water - purified	s47% w/w	Diluent	USP/NF

*As stated by sponsor

Sponsor's proposed indications:

1. For the symptomatic relief of neuralgia associated with the following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed.
2. For the symptomatic management of painful diabetic peripheral polyneuropathy.

Requested shelf life:
36 months when stored below 30°C

Poisons schedule:
Not scheduled

Attachments to evaluation report:

1. Tabulated summary of clinical studies
2. Labels
3. Consumer Medicine Information/Package insert

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ZACIN HP TOPICAL ANALGESIC CREAM 0.075% capsaicin tube

Issues

1. **Amendments to label and CMI/pack insert required.**
2. **Additional information/ assurances regarding manufacturing and starting material specifications required.**
3. **Additional stability data required.**

This is a **NEW PRODUCT** application.

Background

The proposed 0.075% capsaicin cream is indicated for symptomatic relief of post-herpetic neuralgia and diabetic polyneuropathy. One other 0.075% capsaicin cream (Zostrix HP Cream, AUST R 10344) is included on the ARTG. This product was grandfathered and has the indications "*A topical analgesic cream for the management of medically diagnosed painful diabetic neuropathy or postherpetic neuralgia*".

The sponsor of Zacin HP (AFT Pharmaceuticals Pty Ltd) has also submitted an application for a 0.025% capsaicin cream (Zacin OA, OM-2009-00970-3) which is the subject of a separate evaluation report. Another 0.025% capsaicin cream, Zostrix AUST R 19658, is also included on the ARTG.

The indications for the two Zostrix Creams currently on the ARTG have not been fully evaluated.

Product Name

The sponsor proposed the name Zacin HP Topical Analgesic Cream for the product. The sponsor has also submitted an application for registration of Zacin OA Topical Analgesic Cream, which contains 0.025% w/w capsaicin, and is proposed to be indicated for relief of the pain of osteoarthritis.

"Zacin" is very similar to "Zactin", which is the trade name of a range of fluoxetine tablets indicated for the treatment of depression. The different dose forms, indications and schedules of Zacin and Zactin, may make it unlikely that consumers would confuse Zacin and Zactin at the point of use. However, the two names are considered both look-alike and sound alike names, and could be confused at other points in the chain between manufacture and product use, including by health professionals. Therefore the proposed product name "Zacin HP" is considered unacceptable, and the sponsor will be requested to provide an alternative name for the product (and for the related product "Zacin OA".

In terms of differentiating the two product strengths, the "OA" and "HP" parts of the product name are considered acceptable provided the labels of the two products adequately differentiate them.

Efficacy and Safety

Active ingredient

The analgesic properties of topical capsaicin are mediated by depletion of substance P (due to binding of capsaicin to TRPV1[1] receptors on nociceptive neurons and subsequent depolarisation) which leads to desensitisation of small sensory neurons with repeated application.

Data provided

To support the efficacy and safety of the proposed 0.075% capsaicin cream, the sponsor has conducted s47 of 0.075% capsaicin cream for symptomatic relief of painful diabetic neuropathy and post-herpetic neuralgia. The sponsor conducted separate s47 for each indication. Full details of the s47 have been provided. The s47 appear satisfactory. The two indications are discussed separately below.

Discussion – diabetic neuropathy

A total of s47 , plus one further report identified from reference lists. s47 as they related to different doses of capsaicin (0.05%), different dose forms (plaster or nasal spray instead of cream), were not s47 included all neuropathic pain and not just diabetic neuropathy, or were partial reports of a study for which the full report was also retrieved. The exclusion of these s47 is appropriate. The remaining s47 have been provided for review, along with an overview prepared by the sponsor. s47 - are tabulated in Attachment 1.

s47 or unstated) applied four times daily for a minimum of 4 weeks against a placebo cream. One of these s47 included a second open label phase where capsaicin cream was applied four times daily for up to 48 weeks. The s47 compared the efficacy of 0.075% capsaicin cream against an oral treatment, amitriptyline, administered at 25 – 125 mg/day (dose titrated to individual patient need).

s47 are by the same group, and have exactly the same number of subjects, inclusion criteria, treatments, and drop-outs. These two references are reports of the

[1] Transient Receptor Potential V1

same clinical trial – reference 3 reports on additional parameters (functional assessments) that were not included in reference 2.

It is not clear whether any of the s47 [redacted] See under Overall Conclusions for a discussion of this issue.

Efficacy

The primary efficacy criterion in each of the studies was the percentage of patients who showed improvement in the physician's global evaluation. Additional efficacy criteria included improvement in patient-rated categorical pain, and change in pain and pain relief on visual analogue scale (VAS). One study (3) also included a functional assessment of interference with daily activities including eating, sleeping, walking, working, recreational activities and wearing shoes and socks.

All studies demonstrated a greater improvement in all efficacy criteria (except functional assessment involving eating and wearing shoes and socks) in the capsaicin group compared to the placebo group, even against a relatively high placebo effect in some studies (up to 50%). This difference was statistically significant in the majority of studies for the majority of parameters after 2-4 weeks treatment. The study in which capsaicin cream was compared with amitriptyline found that both treatments produced statistically significant improvement in all parameters from baseline, and there was no significant difference between the two groups.

Safety

No systemic adverse events associated with capsaicin cream were reported in any of the studies. All studies reported a high incidence of application site reactions (burning and/or stinging), of mild to moderate severity. The proportion of subjects in the capsaicin groups experiencing these application site reactions was high (up to 63%%) initially, but decreased with repeated treatment. A proportion of subjects in the placebo group (up to 17%) also reported burning/stinging at the application site initially.

Coughing was reported more frequently in the capsaicin group than the placebo group in one study (2) and more frequently than in the amitriptyline group in another study (6). This is a known adverse event associated with use of topical capsaicin cream, and is thought to be due to inhalation of capsaicin particles when the cream is allowed to dry on the skin, and is not adequately rubbed in. Not surprisingly, the overall safety profile of capsaicin cream was better than that of oral amitriptyline.

Blinding

Capsaicin cream initially causes a high incidence of burning/stinging at the application site, which decreases with repeat applications. This burning/stinging may confound blinding in the clinical studies.

Conclusion

The clinical studies provided by the sponsor are all relatively small, with s47 [redacted] treated with 0.075% capsaicin cream in the s47 [redacted] combined. However, the results of all studies are consistent, and demonstrate a (mostly) statistically significant improvement in painful diabetic neuropathy, when applied four times daily. Although application site reactions are common initially, these reduce in incidence with repeated application.

Discussion – post-herpetic neuralgia

A total of s47 as they related to different doses of capsaicin (0.025%), different dose forms (plaster or nasal spray instead of cream), were not controlled trials or meta-analyses, did not provide results on capsaicin treatment, or included all neuropathic pain and not just post-herpetic neuralgia. The exclusion of these s47 is appropriate. The remaining s47 have been provided for review, along with an overview prepared by the sponsor. These s47 - are tabulated in Attachment 1.

Both s47 examined the efficacy of 0.075% capsaicin cream s47 applied 3-4 times daily for 6 weeks against a placebo cream in subjects with severe intractable post-herpetic neuralgia. One of the studies (8) included a second open label phase where capsaicin cream was applied four times daily for up to 2 years.

Neither of the studies used the proposed product. See under Overall Conclusions for a discussion of this issue.

Efficacy

The primary efficacy criterion in each of the studies was the percentage of patients who showed improvement in the physician's global evaluation. Additional efficacy criteria included improvement in patient-rated categorical pain, and change in pain and pain relief on visual analogue scale (VAS). One study (8) also included a functional assessment of interference with daily activities.

Both studies demonstrated a significantly greater improvement in all efficacy criteria in the capsaicin group compared to the placebo group, even against a relatively high placebo effect of up to 35%. This difference was statistically significant from 2 weeks of treatment. The effect in subjects with post-herpetic neuralgia for longer than 12 months was greater than in those whose neuralgia had been present for 6-12 months. In the open label phase of reference 8, pain relief was maintained or increased from the end of the double blind phase in 86% of patients, and decreased in 14%.

Safety

No systemic adverse events were reported in either of the studies. Both studies reported a high incidence of application site reactions (burning and/or stinging), of mild to moderate severity. The proportion of subjects in the capsaicin groups experiencing these application site reactions was high (up to 61%%) initially, but decreased with repeated treatment. A proportion of subjects in the placebo group (up to 33%) also reported burning/stinging at the application site initially.

Coughing was reported more frequently in the capsaicin group than the placebo group in one study (8). This is a known adverse event associated with use of topical capsaicin cream, and is thought to be due to inhalation of capsaicin particles when the cream is allowed to dry on the skin, and is not adequately rubbed in.

Blinding

Capsaicin cream initially causes a high incidence of burning/stinging at the application site, which decreases with repeat applications. This burning/stinging may confound blinding in the clinical studies.

Conclusion

The clinical studies provided by the sponsor are all relatively small, with s47 subjects treated with 0.075% capsaicin cream in the two clinical studies combined. However, the results of both studies are consistent, and demonstrate a statistically significant improvement in post-herpetic neuralgia, when applied four times daily. Although application site reactions are common initially, these reduce in incidence with repeated application.

s47

A s47 of topical capsaicin for chronic neuropathic pain in adults was published in 2009 (10). This review was identified in the sponsor's literature searches, but excluded on the grounds that the meta-analysis covered all forms of chronic neuropathic pain, and not diabetic neuropathy and/or post-herpetic neuralgia separately. While the exclusion of the Cochrane Review is consistent with the sponsor's criteria, since neuropathic pain of various origins has many similarities in pathology and treatments, the conclusions of the review are considered worth examining.

The s47 sought randomised, double blind, controlled studies comparing topical capsaicin -applied 3-4 times daily for at least 6 weeks for low dose (<0.1%) or single application for high dose (8%) - with placebo or other active treatment in adult patients with chronic (>3 months) neuropathic pain of at least moderate intensity. Studies must have at least 10 subjects per treatment arm.

Nine studies fulfilled the entry criteria – 3 in post-herpetic neuralgia, 2 in diabetic neuropathy, and 1 each in surgical neuropathic pain, chronic distal painful polyneuropathy, painful HIV neuropathy and postmastectomy pain syndrome. Two studies used an 8% capsaicin patch, and the others used 0.075% capsaicin cream. Of the seven studies using 0.075% capsaicin cream, six provided dichotomous outcome data. A total of 198 patients were treated with the capsaicin cream and 191 with placebo in these 6 studies. Of these, 41% of the capsaicin patients and 26% of the placebo patients experienced "successful" treatment (improvement in pain to a degree defined in each study). The number needed to treat (NNT) for successful treatment over 6-8 weeks was 6.6 (4.1 to 17), and the relative benefit compared to placebo was 1.6 (1.2 to 2.1).

The s47 concludes that 0.075% capsaicin cream appears to provide some degree of improvement in neuropathic pain conditions with repeated application over a period of 6-12 weeks. However, the limited amount of data and lack of a consistent definition of "successful treatment" mean that estimates for the number of patients achieving meaningful levels of pain relief are not robust.

Overall conclusion

The sponsor has provided published reports of clinical trials in support of the proposed indications. The clinical trials included by the sponsor are of reasonable quality – randomised, double blind (although note comments on blinding above) and controlled and the efficacy parameters in the studies are standard for analgesic efficacy determination. The studies are relatively small, but the results of all the studies are consistent in demonstrating a statistically significant improvement in pain after treatment with 0.075% capsaicin cream (3-4 times daily for at least several weeks) compared to placebo, on a background of relatively high placebo effect.

Although the magnitude of the effect over placebo is not great, the study subjects have chronic pain which, at least in the case of post-herpetic neuralgia, had proven intractable and resistant to other treatments. In such cases, even a moderate improvement in pain may be clinically significant.

The published studies all used a capsaicin cream containing the same concentration of capsaicin as the proposed product. However, it is not clear whether the formulation of the products used in the clinical studies was identical or similar to that of the proposed product, and it is not known what effect different formulations would have on the efficacy or safety of the cream. Capsaicin is not included in the ARGOM list of topical products known to be formulation dependent. However, no evidence has been provided that it is not formulation dependent. The sponsor will be advised that the TGA has concerns over whether the efficacy and safety of capsaicin topical products are formulation dependent, and will be requested to justify the relevance of the submitted clinical studies to the proposed product.

Topical capsaicin cream does not have systemic adverse events. Burning and stinging at the application site are common, but generally decrease with continued use of the cream. Coughing may occur, generally associated with cream left to dry on the skin and not rubbed in. Overall, the safety profile of the cream is reasonable. Burning/stinging is transient, but subjects can cease use of the cream if it is found to be excessive or intolerable.

It is considered that the data provided by the sponsor, combined with references in standard texts such as Martindale and The Handbook of Non-prescription Drugs, which both refer to the use of topical capsaicin as a rubefacient and topical analgesic, support the registration of the product for the proposed indications, subject to a satisfactory response from the sponsor to the issue of formulation dependence.

Indications

The requested ARTG indications are:

"1. For the symptomatic relief of neuralgia associated with the following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed. 2. For the symptomatic management of painful diabetic peripheral polyneuropathy.".

The proposed indications are consistent with the results of the clinical studies, and are acceptable, but should be reworded to remove grammatical errors and to refer to medically diagnosed diabetic peripheral neuropathy (to be consistent with the label claims) to:

"1. For the symptomatic relief of neuralgia following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed. 2. For the symptomatic management of medically diagnosed painful diabetic peripheral polyneuropathy.".

The requested label indications are:

Main label:
"To relieve the pain of diabetic neuropathy.".

Back label:
"For the treatment of medically diagnosed painful diabetic neuropathy or post-herpetic neuralgia (pain following shingles)"

These indications are consistent with the proposed ARTG indications and with the results of the clinical studies, and are acceptable.

Directions for use

The proposed directions for use of the product on the tube and carton label are:

"Adults and children 2 years of age and older: Apply Zacin HP cream to the affected area 3-4 times daily. Zacin HP cream may cause temporary burning on application. This burning is observed more frequently when Zacin HP cream is applied less than 3-4 times daily. After applying Zacin HP cream with fingers, hands should be washed immediately, unless the hands are being treated. ".

The directions for use are consistent with the usage of 0.075% capsaicin cream in the published clinical trials and are acceptable. However, the recommended patients age group of adults and children over 2 years of age is not consistent with the subjects used in the clinical studies, nor with the pack statement "*Not recommended for use on children*". The recommended patient population should be amended to "*Adults*".

Also, additional information (such as how much to use at each application, and the fact that it may take several weeks of treatment to achieve meaningful pain relief, and a month of treatment to achieve maximum effect) is included in the CMI/pack insert. The directions for use on the tube and carton label should be amended to include "*For further information on how to use this product see the pack insert*" or similar.

Labelling

The following changes to the tube and carton labels are recommended:

1. As indicated above, the directions for use on the tube and carton label should be amended to include "*For further information on how to use this product see the pack insert*" or similar, and the patient population should be amended to remove reference to children.

2. The storage instruction on the label is "Store below 25°C" but the requested storage instruction in the application form is "Store below 30°C". The real time stability studies were conducted at 30°C, and therefore the label should be amended.

3. The presence of the preservative, benzyl alcohol, should be declared on the tube and carton labels.

The labelling otherwise complies with the requirements of the TGO 69, SUSDP, RASML, ARGOM and the Therapeutic Goods Advertising Code. Reference to not bandaging tightly is consistent with the label of Zostrix and is therefore acceptable.

Consumer medicine information (CMI) document

The CMI is to be included as a package insert.

The following changes to the CMI / package insert are recommended:

1. Under "What is in this leaflet", "It summaries..." should be amended to "It summarises.."

2. Under "What Zacin HP is used for and how it works" the concentration of capsaicin should be amended to 0.075%.

3. Under "How to use Zacin HP" the reference to "Zaxon" should be amended to "Zacin".

4. The frequency of use of the product should be consistent between the product label and the CMI. Therefore either both should refer to use 3-4 times daily, or both should refer to use 4 times daily.

5. References in the CMI to rubbing into the affected joint should be amended to refer to rubbing into the affected area, since not all cases of diabetic neuropathy or post-herpetic neuralgia are in joints. The reference to the amount of product to use should also be amended so that it does not refer only to joints, as should the reference to arthritic hand joints (in the section about washing residue off hands).

6. Although the CMI contains references to not using the product on broken skin, given that the product is intended for use after an episode of shingles, it should be recommended to the sponsor that the CMI include a specific reference to not using the product for pain after shingles until the open shingles lesions have healed.

7. The storage condition should be amended to "Store below 30°C" consistent with the stability data.

8. The reference to not using tight bandages over the cream should be moved from the Storage section of the CMI to under "Things you must not do".

9. A reference to coughing (as noted in the clinical studies) should be included in the "Side Effects" section of the CMI and also under "How to use it" (as with reference to the burning sensation). If the sponsor wishes, a statement indicating that coughing may be minimised if the cream is not allowed to dry on the skin (or similar) could be included.

10. The instruction "Do not stop using Zacin HP, or lower the dosage, without checking with your doctor" is not necessary and not appropriate for a topical analgesic, even one that may take several weeks to produce an effect. The statement should be removed. If the sponsor wishes, it could be replaced with a statement to the effect that pain may return if treatment is stopped, or similar.

11. Under Product Description, the sponsor should include a description of the cream and the pack sizes available (for instance, Zacin HP is a viscous white cream which is available in 25 g and 45 g tubes).

Quality

Manufacture

The proposed manufacturing site is s47 [redacted] – all steps of manufacture. The sponsor has provided a GMP Clearance certificate that expired in November 2010. The sponsor will be requested to provide a current GMP Clearance certificate.

The submission includes details of the steps of manufacture and a brief outline of the method of manufacture. In accordance with OTC Section policy (see SOP 'Pre-market evaluation), this information has been filed for reference without evaluation.

The sponsor has provided process validation data for three production bulk batches. Consistent with usual practice, the sponsor will be requested to provide a written assurance that the manufacturing process validation has been conducted according to the requirements of the Code of Good Manufacturing Practice (the *Therapeutic Goods (Manufacturing Principles) Determination No. 1 2009* contains a definition of 'the Code').

Formulation

The amount of capsaicin in the finished product is 0.075% w/w. The amount of capsaicin in the capsaicin API in NLT s47 %, and the actual amount of API added to the formulation varies depending on the actual concentration of capsaicin in the API.

The base formulation for s47 [redacted] – the only difference is in the s47 [redacted] in the finished product.

The application form lists glyceryl monostearate as an ingredient in the cream at a concentration of s47 % w/w. However, the pharmaceutical development section of the dossier indicates that the emulsifier in the product is actually a mixture of glyceryl monostearate and PEG-100 stearate. It appears that this mixture is purchased as s47 [redacted] This ingredient is included on the ARTG with proprietary ingredient number s47 [redacted] The ratio of glyceryl monostearate and PEG-100 stearate in the mixture is not stated.

The sponsor will be requested to confirm that the emulsifier in the product is actually s47 [redacted] and not glyceryl monostearate.

The formulation of the proposed product is compared to that of the currently registered Zostrix HP Cream ARTG 10344 below.

Formulation comparison of Zacin HP Cream and Zostrix HP Cream

Ingredient	Zacin HP	Zostrix HP
Capsaicin	0.075% w/w	0.075% w/w
Benzyl alcohol	s47 % w/w	s47 % w/w
Sorbitol solution 70% non-crystallising	s47 % w/w	s47 % w/w
Isopropyl myristate	s47 % w/w	s47 % w/w
Cetyl alcohol	s47 % w/w	s47 % w/w
Paraffin – soft white	s47 % w/w	s47 % w/w
glyceryl monostearate/PEG-100 stearate	s47 % w/w[1]	s47 % w/w[1]
Water - purified	s47 % w/w	s47 % w/w

1. The glyceryl monostearate/PEG-100 stearate mix in Zacin is s47 [redacted] while in Zostrix it is s47 [redacted] The quantitative composition of the two proprietary ingredients is not known.

Starting material specifications

The raw material specifications for capsaicin and purified water comply with the USP monograph requirements. The raw material specifications for all other ingredients except for glyceryl monostearate/PEG 100 stearate comply with the BP monograph requirements.

The sponsor applies in-house specifications to glyceryl monostearate/PEG-100 stearate as follows:

Glyceryl monostearate/PEG-100 stearate: s47 [redacted]

The sponsor will be requested to confirm that the glyceryl monostearate and PEG-100 stearate from which the mixture is composed comply with compendial monographs. The sponsor will also be requested to show that the raw material specification for the mixture is capable of differentiating between different ratios of glyceryl monostearate and PEG-100 stearate.

The starting material specifications are satisfactory except as noted.

Finished product specifications

The proposed finished product specifications are as tabulated below.

Test	Batch release limits	Expiry limits
Description	Viscous white cream with characteristic odour	
Identity of capsaicin	Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the assay	
Content of capsaicin (HPLC)	s47 [redacted]	s47 [redacted]
Content of capsaicin and dihydrocapsaicin (HPLC)	s47 [redacted]	s47 [redacted]
Content of other capsaicinoids (HPLC)	s47 [redacted]	s47 [redacted]
Content of benzyl alcohol (HPLC)	s47 [redacted]	s47 [redacted]
pH at 25°C	s47 [redacted]	s47 [redacted]
Viscosity at 25°C	s47 [redacted]	s47 [redacted]
Microbial limit test Total viable aerobic count Enterobacteria *Pseudomonas aeruginosa*	s47 [redacted]	

Test	Batch release limits	Expiry limits
Staphylococcus aureus	s47 [redacted]	
Minimum fill 25 g tube 45 g tube	s47 [redacted]	-

The product is not the subject of a specific BP or USP monograph.

The limits for the content of dihydrocapsaicin + capsaicin, and other capsaicinoids, are based on the limits in the capsaicin raw material s47 [redacted]

The microbial limits should be amended to be consistent with TGO 77.

The finished product specifications are satisfactory.

Test Methods and Analytical Method Validation

Assay of capsaicin and capsaicinoids

Capsaicin and capsaicinoids are assayed using a single reverse phase HPLC method, with UV detection at 281 nm. The retention time of capsaicin is approximately s47 [redacted] minutes, while the retention time of dihydrocapsaicin is approximately s47 [redacted] minutes and other capsaicinoids approximately s47 [redacted] minutes.

The assay is s47 [redacted], except that s47 [redacted] g of sample is used in the Zacin OA assay, and s47 [redacted] g is used in the assay of Zacin HP.

The supporting validation data are summarised in the table below:

Parameter	Results/Comment
Accuracy	Determined at s47 [redacted] and s47 [redacted]% expected/limit for capsaicin, dihydrocapsaicin and capsaicinoids. Recovery s47 [redacted] %, s47 [redacted] s47 [redacted]% and s47 [redacted] respectively.
Precision	Repeatability: %RSD s47 [redacted] (capsaicin) s47 [redacted] (dihydrocapsaicin), s47 [redacted] (capsaicinoids) Intermediate precision: meets criteria (capsaicin, dihydrocapsaicin and capsaicinoids)
Linearity	Determined over range s47 [redacted] % of expected/limit for capsaicin, dihydrocapsaicin and capsaicinoids. Correlation coefficients s47 [redacted] and s47 [redacted] respectively
Specificity (excipients and degradants)	Determined in relation to excipients, between capsaicin, dihydrocapsaicin and capsaicinoids, and under conditions of forced degradation.
Quantification Limit (related substances)	LOD for capsaicinoids (based on signal to noise ratio of at least 3:1) is s47 [redacted] % w/w in finished product.

Robustness, ruggedness, solution stability and system suitability were also assessed and found acceptable.

The sponsor should be requested to provide the limit of quantitation for the assay of capsaicinoids, and not just the limit of detection. Calculations and results used to determine the LOQ should also be provided. The sponsor should be reminded that the LOQ of the assay should be considered in terms of the capsaicinoid limits in the finished product specifications, to ensure that the assay is capable of detecting changes in the capsacinoid content.

The test method and validation are satisfactory except as noted.

Assay of benzyl alcohol

Benzyl alcohol is assayed using a reverse phase HPLC method with detection at s47 nm. The retention time of benzyl alcohol in the assay is approximately s47 minutes.

The supporting validation data are summarised in the table below:

Parameter	Results/Comment
Accuracy	Determined at s47 and s47 % nominal. Recovery s47 %
Precision	Repeatability: %RSD s47 Intermediate precision: met acceptance criteria
Linearity	Determined over range s47 % nominal. Correlation coefficient = s47
Specificity (excipients and degradants)	Determined in relation to all other cream ingredients, and under conditions of forced degradation.

Robustness, ruggedness, solution stability and system suitability were also assessed and found acceptable.

The test method and validation are satisfactory.

Container

The product is to be packaged in lacquered aluminium tubes with polyethylene caps, with are further packed into cardboard cartons. Pack sizes of 25 g and 45 g are proposed.

Both pack sizes are unscheduled.

There are no queries regarding the proposed container.

Stability

In support of the proposed shelf life of 36 months when stored below 30°C in aluminium tubes the sponsor has provided stability data generated using the batches tabulated below. The formulation and container used in the studies are identical to those proposed for registration, and the batches were full production size (100 kg).

Batch No.	Duration of storage (months)	
	30°C/75%RH	40°C/75%RH

00132907	s47	s47
1046B807	s47	s47
0892A807	s47	s47

The parameters tested and the results from these tests are summarised in the following table:

Test	Results/Discussion
Description	s47
Content of capsaicin	s47
Content of capsaicin and dihydrocapsaicin	s47
Content of other capsaicinoids	s47
Content of benzyl alcohol	s47
pH at 25°C	s47
Viscosity at 25°C	s47
Microbial limit	s47
Preservative efficacy:	s47

According to the date of initiation of the stability studies, at least 24 months real time data should be available on all three batches. The sponsor will be requested to submit these updated stability data. There are insufficient data points in the real time data provided to date to make an adequate assessment of any trends in the real time stability data.

Summary, conclusions and recommendations

To date only 6 months real time and 6 months accelerated stability data have been provided. These data are insufficient to support the requested shelf life of 36 months when stored below 30°C, and currently only support a shelf life of 12 months at this storage temperature. However, additional stability data should be available by now, and the sponsor will be requested to submit this to support the requested shelf life.

References

1. s47 et al. s47

2. s47

3. s47

CONFIDENTIAL

4. s47 et al. s47 [redacted]

5. s47 et al. s47 [redacted]

6. s47 et al. s47 [redacted]

7. s47 et al. s47 [redacted]

8. s47 et al. s47 [redacted]

9. s47 et al. s47 [redacted]

Tabulated summary of clinical studies

Attachment 1

Tabulated summary of published references provided in support of efficacy and safety of s47

Ref	Study design	Subjects	Treatments	Parameters	Efficacy results	Safety results
s47						
1	s47	s47	s47	s47	s47	s47
2	s47	s47	s47	s47	s47	s47
3	s47	s47	s47	s47	s47	s47

Attachment 1

Ref	Study design	Subjects	Treatments	Parameters	Efficacy results	Safety results
4	s47	s47	s47 s47	s47	s47	s47
5*	s47	s47	s47	s47	s47	s47

Attachment 1

Ref	Study design	Subjects	Treatments	Parameters	Efficacy results	Safety results
6	s47	s47	s47	s47	s47	s47
Studies on post-herpetic neuralgia						
7	s47	s47	s47	s47	s47	s47

Ref	Study design	Subjects	Treatments	Parameters	Efficacy results	Safety results
8	s47	s47	s47	s47	s47	s47
5*	s47	s47	s47	s47	s47	s47

s47

* The meta-analysis separately analysed studies in diabetic neuropathy, osteoarthritis, post-herpetic neuralgia sand psoriasis. The results relating to diabetic neuropathy and post-herpetic neuralgia are included separately in this tabulated summary.

Note: Studies 3 and 4 are apparently the same study