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Pigmerise™ FAQs and answers

Created by FAD project team



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Introduction

Pigmerise™ - innovation in skin repigmentation is a global concept. The ready-to-use marketing material template and other supportive documentation can be found on the Fagron Brand Portal. The Pigmerise™ FAQ is based on the questions that have been received by all FACOs since the launch of the FAD-Pigmerise™ concept. All questions have been reviewed by the FAD project team.

We wish you a lot of success with the launch and sales of the Pigmerise™ concept.

FAD project team
December 2016



Technical questions concerning compounding

1. What is the difference between piperine powder and Pigmerise™?

- Piperine, the main alkaloid from black pepper dry extract, is available in powder form, and must be solubilized in alcohol in order to be compounded in a topical vehicle. The presence of alcohol in the topical formulation increases the risk of a skin irritation and reduces the treatment compliance.
- Pigmerise™ is a natural extract obtained from the fruits of black pepper (*Piper nigrum* L.). It is a natural phytocomplex containing alkaloids and volatile oils in an oleoresin. Pigmerise™ contains a high concentration of piperine, one of the major alkaloids of *Piper nigrum* L..
- Pigmerise™ is a water-soluble (contains polysorbate 80 that helps to solubilize Pigmerise™) and can be easily compounded in Fitalite™. There is no need for the use of alcohol in the compounding process, reducing the risk of skin irritation.

2. Can I replace Pigmerise™ for piperine powder?

No, because of following reasons:

- Piperine powder requires alcohol to be dissolved prior to be added in a topical vehicle. The presence of alcohol can lead to increased skin irritation once applied on the skin.
- Pigmerise™ is an oleoresin that can be easily compounded and incorporated into water, oil or vehicle, without the use of alcohol.



Technical question concerning stability

1. What is the stability of the compounded preparation Pigmerise™ in Fitalite™?

Physical and microbial stability studies show that Pigmerise™ in Fitalite™ remains stable at room temperature (15-25 °C) for 6 months after compounding.

2. Can Pigmerise™ be used in vehicles other than Fitalite™?

The stability and skin irritation studies have been performed only with gel cream Fitalite™. The use of other vehicle is the responsibility of doctor and pharmacist. Besides, the Fitalite™ contains natural phytosomes that enhance delivery of APIs and DCIs into deeper skin layers, which is necessary for Pigmerise™'s efficacy.

3. Can I use a different packaging other than airless dispenser?

The use of the airless dispenser is recommended to avoid contact of the product with air, as Pigmerise™ contains volatile oils. Therefore, one should always use a packaging that ensures minimal contact with air.

4. Is it necessary to store the compounded product in the refrigerator?

It is not necessary to store it in the refrigerator. The formulation of Pigmerise™ in Fitalite™ is stable for 6 months at room temperature. In warmer regions, it may be recommended to store the product refrigerated.

Scientific questions concerning treatment of hypopigmentation disorders with Pigmerise™ in Fitalite™

1. What is Pigmerise™?

Pigmerise™ is a natural extract obtained from the fruits of black pepper (*Piper nigrum* L.). It is a natural phytocomplex with alkaloids and volatile oils in an oleoresin. Pigmerise™ contains a high concentration of piperine, one of the major alkaloids of *Piper nigrum* L..

2. What is the mechanism of action of Pigmerise™?

Piperine, the main component of Pigmerise™, stimulates melanocytes proliferation and induces the formation of melanocyte dendrites¹⁻⁴. This leads to melanogenesis and promotes skin repigmentation in hypopigmentation disorders¹⁻⁶. Piperine acts as a UV filter and does not bind to cellular DNA and does not trigger the development of melanoma⁷.

3. Can Pigmerise™ in Fitalite™ be used for the treatment of hypomelanosis guttata?

Yes, Pigmerise™ stimulates melanocyte proliferation and dendrite formation, resulting in skin repigmentation¹⁻⁶. Pigmerise™ is indicated for the treatment of a wide range of hypopigmentation disorders such as vitiligo and idiopathic guttate hypomelanosis.

4. What is the advised dosage and use of Pigmerise™ in Fitalite™?

The recommended concentration is 20% of Pigmerise™ in Fitalite™.

Formulation	
Pigmerise™	10 g
Fitalite™	qs 50 g
Airless dispenser (50 ml)	1 unit

Instructions for use

- Apply Pigmerise™ in Fitalite™ gel cream on the affected area once daily at night.
- A thin layer of the preparation should be applied to avoid a transient burning sensation. Use the fingertip unit system to determine the amount of formulation required for the affected area.
- Wait approximately 20 minutes before applying any other topical treatments or cosmetics.



- Rinse the Pigmerise™ in Fitalite™ preparation off the affected area before exposing to UVR if applicable (in case of combined UVR therapy or exposure to sunlight).
5. **Do you recommend the treatment of Pigmerise™ in Fitalite™ with or without UV? Or both options?**

Pigmerise™ is safe and effective with or without UVB therapy. Pigmerise™ can be used during UV therapy to increase skin repigmentation. Pigmerise™ treatment does not influence the general UV treatment protocol. The UV therapy should always be determined by the treating physician for each individual, according to the patient's clinical evaluation. Please note that generally UV treatment is not recommended during the active phase of vitiligo when depigmentation occurs.

Pigmerise™ in Fitalite™ should not be applied before exposing to UV therapy or exposure to sunlight, as piperine acts as a UV filter (studies show the activity of piperine in preventing skin cancer and protection against melanoma). The preparation should be applied on the affected area once daily, at night. The patient should rinse the Pigmerise™ in Fitalite™ preparation off the affected area before exposing to UVR if applicable (in case of combined UVR therapy or exposure to sunlight).

6. **Can Pigmerise™ be applied in the area around the eyes and mouth? How do you recommend to apply the cream in the area around the eyes and the mouth?**

Yes, this is possible. One of the added values of Pigmerise™ in Fitalite™ is that there is no need for alcohol use in the compounding process, allowing application on sensitive skin areas. It is recommended to apply the formulation of Pigmerise™ in Fitalite™ first to the areas where the skin is thick. Subsequently a thinner layer can be applied to the eyelids, genitals, and margins of the lips and mouth.

7. **Does the formulation Pigmerise™ in Fitalite™ irritate the skin?**

The skin irritation study performed by the University of Ferrara shows that Pigmerise™ in Fitalite™ under occlusive conditions is not irritating to the skin, making it a safe alternative for the treatment of hypopigmentation disorders.

8. **What might be the side effects of Pigmerise™?**

A transient (5-30 minutes) burning sensation can occur. A thin layer of the preparation should be applied to avoid this. Use the fingertip unit system to determine the amount of formulation required for the affected area.

9. **Can Pigmerise™ be used by children?**



There are no studies on the use of Pigmerise™ in children however the formulation of Pigmerise™ in Fitalite™ has been designed to be applied on sensitive skin. According to the clinical experience of Dr. Menchini (KOL of FAIT), it can be used for the treatment of vitiligo in children ≥ 2 years.

10. Can Pigmerise™ be used during pregnancy?

There are no studies on the use of Pigmerise™ during pregnancy.

11. What is the advantage of Pigmerise™ over khellin?

The advantages are:

- Pigmerise™ is safe and effective in promoting the repigmentation of affected areas, with or without the need for UVB therapy. On the other hand, khellin requires phototherapy (UVA) for the same purpose.
- Pigmerise™ is safe, with no carcinogenic effect, since scientific evidence shows that piperine does not bind to cellular DNA and protects against melanoma.
- Khellin, despite being safer than psoralens, have a low rate of binding to cellular DNA.
- Pigmerise™ is well tolerated when compared to khellin, and does not promote side effects such as hyperpigmentation around the lesion and blistering.

12. What is the difference between Pigmerise™, khellin and tacrolimus?

Pigmerise™	Khellin	Tacrolimus
Piperine and its alkaloids stimulate the proliferation of melanocytes that are located deeply in the epidermis, leading to the production of melanin.	It has a chemical structure similar to psoralens. It promotes photosensitivity of the skin. The UV radiation, applied in a sequency, activates the proliferation of melanocytes and melanin production.	It is immunosuppressive. It controls cells autoimmune system and it does not allow the destruction of the melanocytes.
It induces the pigmentation with or without the use of phototherapy (UV).	Requires phototherapy (UVA radiation) for pigmentation effect.	It reduces the attack of the immune system and the destruction of the melanocytes. It is not involved in the skin repigmentation process.
The main component of Pigmerise™, according to the latest scientific evidence, does not bind to the cellular DNA. It is the	Binds to the cellular DNA on a smaller scale (when compared to psoralens) and creates a risk of skin cancer.	It does not cause skin atrophy as corticosteroids.



only product that while it stimulates and promotes skin repigmentation, it does not trigger the risk of developing skin cancer.		
Mild and transient side effects (redness and and burning sensation) can be observed in sensitive areas.	There are side effects such as pigmentation of areas adjacent to the spot and occurrence of blisters and rashes.	Sides effects such as an itching and burning sensation (>10%). Erythema, pain, irritation, rash, alcohol intolerance (1-10%)

13. What is the difference between compoundig with Pigmerise™, methoxaslen and tacrolimus?

Pigmerise™	Methoxsalen	Tacrolimus
Wear gloves and glasses glasses when compounding, no further protection needed.	Methoxsalen should be compounded in a safety cabinet and respirators, safety glasses and gloves are advised to be used. Moreover methoxsalen can influence the fertility, therefore pregnant, breastfeeding women or women and men with a desire to have kids can not compound with this product.	Tacrolimus monohydrate should be compounded in a safety cabinet and respirators and gloves are advised to be used. Moreover tacrolimus is suspected to harm an unborn baby, therefore pregnant or breastfeeding women can not compound with this product.

14. Is a prescription required for Pigmerise™ in Fitalite™?

A prescription can be required depending on the country. Skin diseases need to be treated by a physician. Vitiligo, for example, is a chronic disease that has no cure and the current treatments are focussed on the improvement of the symptoms. Due to the complexity of the treatment of hypopigmentations disorders it is recommended that these patients visit a dermatologist.

15. In The case study performed by Dr.Menchini patients were treated with UVB therapy combined with Pigmerise™ in Fitalite™. What sort of UVB therapy was used?

Dr. Menchini studied 20 patients aged between 18 and 62 years, suffering from bilateral vitiligo. Patients were treated topically with Pigmerise™ in Fitalite™ once-daily, combined with NB-UVB (311 nm) therapy, three times a week, for six months.



16. Were the case studies conducted during the summer or winter?

Menchini G, et al. Testing a piperine cream with and without ultraviolet B phototherapy in 75 patients affected by bilateral vitiligo, GISV- Italian Group for the Study and Treatment of Vitiligo. 2009. This study lasted 10 months, from July 2008 to May 2009.

17. Once the treatment with Pigmerise™ in Fitalite is stopped in the areas that have been repigmented by the treatment, will these same spots become depigmented again?

There is no cure for vitiligo, and Pigmerise™ treatment also does not provide a cure for this disease. The application of Pigmerise™ in Fitalite™ promotes the formation of melanin, and consequently, repigmentation. Like for all other treatments for vitiligo, when the treatment is halted, the depigmentation can occur in the treated areas, or some new depigmented spots can be formed. This depends on each patient, and the course of development of this disease. It is difficult to be predicted.

18. Can Pigmerise™ be used by patients on homeopathic treatment?

During the homeopathic treatment the use of certain substances, such as camphor and menthol, has to be avoided. Some essential oils, like eucaliptus, citronela, thuja, lavanda or mentha oil, also should not be used during this treatment. For a black pepper (*Piper nigrum* L.) oil no literature is citing any restriction of its use during homeopathic treatment.

19. Can Pigmerise™ 20% in Fitalite compounded medication be applied to large affected areas?

In the study conducted by Dr Menchini, the extension of areas affected was 5-70%, and with duration of the treatment of 6 months, no adverse effect has been reported.

20. Do the patients need to apply sunscreen cream on the affected areas after the application of Pigmerise™ formula?

The application of formulation containing Pigmerise™ should be done during the night, and the area treated should be washed in the morning. If the area of vitiligo lesions is located on the body parts that are sun exposed, and not covered by clothes, the use of sun protection is indicated, as for all other sun exposed areas of a skin.

References

1. Lin Z, et al. Stimulation of mouse melanocyte proliferation by Piper nigrum fruit extract and its main alkaloid, piperine. *Planta Med.* 1999 Oct;65(7):600-3.
2. Lin Z, et al. Amides from Piper nigrum L. with dissimilar effects on melanocyte proliferation in-vitro. *J Pharm Pharmacol.* 2007 Apr;59(4):529-36.



3. Faas L, et al. In vivo evaluation of piperine and synthetic analogues as potential treatments for vitiligo using a sparsely pigmented mouse model. *Br J Dermatol.* 2008 May;158(5):941-50
5. Menchini G, et al. Testing a piperine cream with and without ultraviolet B phototherapy in 75 patients affected by bilateral vitiligo, GISV- Italian Group for the Study and Treatment of Vitiligo. 2009.
6. Menchini G. Fitocomplesso da pepe nero in crema gel liposomiale nel trattamento della vitiligine bilaterale: studio su 20 casi. 2016.
7. Soumyanath A, et al. UV irradiation affects melanocyte stimulatory activity and protein binding of piperine. *Photochem Photobiol.* 2006 Nov-Dec;82(6):1541-8.



Marketing related questions

1. What kind of materials are available to promote the Pigmerise™ concept?

- Concept brochure
- Compounding instructions
- Fagron Academy presentation

The Pigmerise™ marketing materials can be downloaded from the Fagron Brand Portal. The compounding instructions are available on Compounding Matters.

2. What are the USPs of the treatment with Pigmerise™ in Fitalite™?

The USPs are:

- Piperine derived from black pepper is difficult to compound with, as it usually is in the form of dry extract. Pigmerise™ is a water-soluble oleoresin that can be easily compounded in Fitalite™.
- As high piperine concentrations are required for an effective treatment, prior solubilization of piperine in alcohol is usually needed. The use of alcohol in topical preparations can cause skin irritation and reduced patient compliance. Moreover these preparation cannot be applied on difficult to treat areas (around the eye and mouth for example). When compounding with Pigmerise™, there is no need for alcohol use in the process, allowing application on sensitive skin areas. This is further supported by the skin irritation study performed by the University of Ferrara that show that Pigmerise™ in Fitalite™ under occlusive conditions is not irritating to the skin, making it a safe alternative for the treatment of hypopigmentation disorders.
- Melanocytes are cells difficult to reach as they are localized in a deep area of the skin. Fitalite™ contains natural phytosomes that enhance delivery of APIs into deeper skin layers.

