Dear colleagues,

Pentravan® was introduced as a Global Trademark in 2012. Since then we have reached great sales numbers globally, but a lot more can be achieved!

The purpose of this document is to provide you with an overview of all information available to support you and your customers in the use of Pentravan®. The Pentravan® global asset kit is also available online for downloading. The global asset kit is uploaded to the Fagron Brand Portal, accessible through https://fagron.getbynder.com/media/ #PentravanGlobalAssetKit. Here you will find the contents of this document, technical information, formulations, reference articles, input for creating your marketing materials, etc.

Pain management is an area in which transdermal creams have a significant added value. Since 2016 a new vehicle has been developed specifically for pain management, this vehicle will replace Pentravan® in this therapeutic area.

Orders

- 50 g sample jars Pentravan® can be produced upon request, a formal quotation will be given by Herkel.
- Orders for 500 g jars with Pentravan® should be directed to Herkel. The transfer price for the 500 g jars is EUR 5.97 (ex works Herkel).

If you have questions about Pentravan®, please contact Fagron GMI by e-mail: globalinnovation@fagron.com or phone: +31 88 33 11 283.

Fagron GMI

Fagron Group BV - Lichtenauerlaan 182, 3062 ME Rotterdam - The Netherlands - Tel. +31 (0)88 33 11 288 - Fax +31 (0)88 33 11 210
KvK 24183722 - VAT NL 8017.27.443.B.01 - ING 67 80 83 533 - IBAN NL61INGB 0678 083533 - BIC INGBNL2A

FACTSHEET PENTRAVAN®

INTRODUCTION

Transdermal delivery
Transdermal delivery of drugs is effective and used to treat many different conditions. Transdermal drug delivery can be "individualized" for each patient by changing the drugs used, their concentrations, and the formulation. This type of drug delivery is routinely used for delivery of hormones, pain medication, nonsteroidal anti-inflammatory drugs (NSAIDs), antinauseant medications, and many others.

Transdermal delivery involves the passage of therapeutic quantities of drug substances through the skin and into the general circulation for systemic effects. For transdermal drug delivery, it is considered ideal for the drug to migrate through the skin to the underlying blood supply without buildup in the dermal layers. Different transdermal drug products (e.g. gels, creams, patches, ointments) are on the market, and evidence of actual percutaneous drug absorption may be found through one or all the following:

- Measurable blood levels of the drug.
- Detectable excretions of the drug and/or its metabolites in the urine.
- Clinical response of the patient to the therapy.[1]

"Transdermals: the skin as part of a drug delivery system" (Allen, L.V. Jr. *International Journal of Pharmaceutical Compounding;* 15 (4). July/August 2011.) provides background information concerning transdermal delivery systems and is included in appendix 1.

Pentravan®
Pentravan® (*penetra*tion enhancing *van*ishing cream) is a transdermal delivery system for drugs (active pharmaceutical ingredients; APIs) and is intended for use as a cream base for pharmaceutical compounding. It is a ready-to-use base that allows the pharmacist to easily compound a transdermal cream in three steps (see chapter "Method of preparation" on page 10). Pentravan® was developed by Fagron US and has a proven and an impressive track record. After a successful introduction in the USA in 2008, Pentravan® was introduced on the Brazilian market in 2011. In February 2012 it has been decided to launch Pentravan® in Europe in June 2012.

Pentravan® is an oil-in-water emulsion with a liposomal matrix that uses the same penetration enhancing ingredients as those used in the Pluronic Lecithin Organogel (PLO) (see next page), but establishes a greater rate and extent of absorption of the drug. Therefore, more of the drug will become available in a shorter time to establish the effect of the therapy. Besides that, Pentravan® is a true vanishing cream, leaving no sticky residue and providing a cosmetically elegant skin feel. Unlike with PLO, there is no need to cover the area of application to prevent transferring of the cream and to ensure effectiveness of therapy. It is preserved and fragrance free.

Transdermal absorption of a drug generally results from direct penetration of the drug through the stratum corneum (SC), a 10 to 15 µm thick layer of flat, partially desiccated, nonliving tissue. The SC is composed of approximately 40% protein (mainly keratin) and 40% water, with the balance being lipid, principally as triglycerides, free fatty acids, cholesterol, and phospholipids. The lipid content is concentrated in the extracellular phase of the SC and

forms to a large extent the membrane surrounding the cells. After application on the skin, the drug molecules that are dispersed within the liposomes of Pentravan® penetrate the SC through the intercellular channels. Once through the SC, drug molecules may pass through the deeper epidermal tissues and into the dermis. When the drug reaches the vascularized dermal layer, it becomes available for absorption into the systemic circulation.[1]

Pentravan® Plus is a related vehicle and is a higher viscosity version of Pentravan®; it uses the same liposomal technology as Pentravan®, but with additional emulsifiers to allow for incorporation of higher concentrations (>25%) of APIs and solvents. Pentravan® Plus vanishes into the skin, enhancing penetration of the APIs without leaving a sticky residue on the skin. Therapeutic compliance and patient satisfaction therefore can be significantly improved with Pentravan® Plus. Pentravan® Plus is currently only available in the US.

Pluronic Lecithin Organogel (PLO)
PLO is a base formulation used in countries like the United States and Brazil. It has been used by compounding pharmacists for topical and systemic delivery of medications through the skin since its introduction in the 1990s. PLO has been utilized to deliver different APIs; from NSAIDs to hormones. In the European countries PLO is less known and less used in compounding.

PLO is a transdermal system with the coexistence of an organic and an aqueous phase in a structurally well-defined micellar network, thus having hydrophilic and lipophilic characteristics. The organic phase, which consists of lecithin solution, undergoes spontaneous gelation after incorporation with pluronic aqueous solution. PLO can partition with the skin and enhance transport of drug molecules into and across the skin. Pentravan® uses the same penetration enhancing ingredients as those used in PLO, but establishes a greater rate and extent of absorption of the drug[2], as shown by an in vitro study published in the May/June 2012 edition of the International Journal of Pharmaceutical Compounding (IJPC). The full article *"In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream"* (Lehman, P.A., Raney, S.G. IJPC, Vol. 16 (43). May/June 2012.) is included in appendix 2. In this article you will find two graphs depicting the results of the study in a visual way. A summary of this study can be found in chapter "In vitro absorption study" on page 16.

The method of preparation of PLO is extensive. To prepare PLO, the oil and aqueous phase need to be mixed using a high-shear mixing method - for example, using two syringes, connected by a luer lock or by using an electronic pestle and mortar. Besides that, the aqueous phase needs to be cold (i.e. 0˚C), while the oil phase should be at room temperature.[2] In contrast, with Pentravan®, a transdermal cream that can be compounded in three simple steps (see chapter "Method of preparation" on page 10).

With the original PLO design, in order to ensure safe and effective use, the site of application needs to be covered to prevent the medication from transferring to clothing and other individuals during the time of absorption and thus decreasing the effect of the therapy.[2] With Pentravan® there is no need to cover the area of application, since it is a vanishing cream that leaves no sticky residue and therefore is more patient friendly.

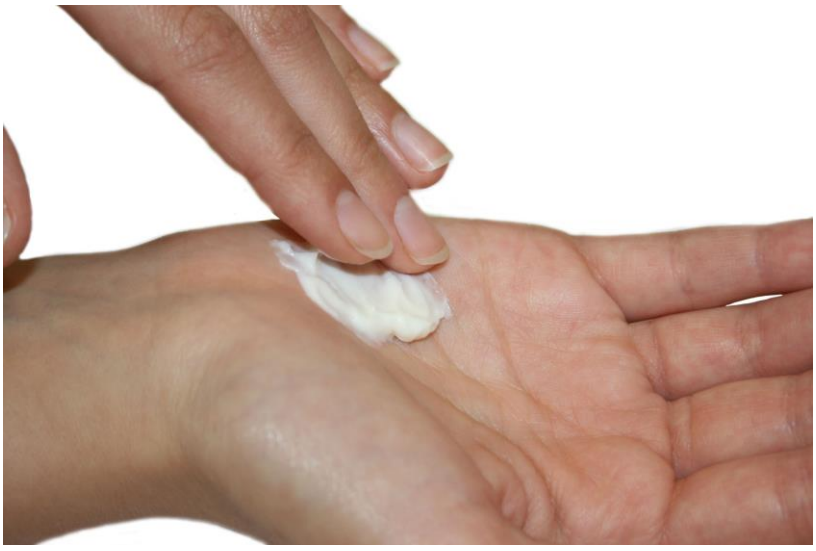
Other transdermal bases

Besides Pentravan® and PLO, other vehicles for compounding transdermal creams or gels that are available are:

- Vanpen® (short for vanishing penetrate): contains an ester and an amide that assists liposome formation to ease the transport of drug through the skin.
- Lipoderm®: transdermal base gel.
- Lipovan® (ours): a liposomal vanishing cream base. The liposomes are manufactured from highly enriched soybean phospholipids. For topical use only. Fragrance, dye, and paraben free.
- Lipobase® (ours): a water removable (vanishing cream type) oil-in-water emulsion base containing natural oils and liposomes in a gel matrix. Does not contain petrolatum or mineral oil. Fragrance, dye, and paraben free.
- Phytobase® (ours): an all-natural, innovative, transdermal cream for a more natural approach to hormone replacement therapy. It is an ultra-light, hydrophilic gel-cream with unique antioxidant and skin moisturizing properties. Ideal for low-concentrations of a wide variety of active pharmaceutical ingredients (APIs), Phytobase™ Cream Base is a unique solution to compounding challenges.

In contrast to Pentravan® and PLO, the bases mentioned above are composed of natural liposomes. It is because of this, that the price of these products is about three fold higher than the price of Pentravan®. Therefore, the demand for these products by pharmacists is limited.

ADVANTAGES / USPs



Advantages/USPs of transdermal drug delivery

Fagron Group BV - Lichtenauerlaan 182, 3062 ME Rotterdam - The Netherlands - Tel. +31 (0)88 33 11 288 - Fax +31 (0)88 33 11 210
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- Although proven successes in Brazil and the United States, transdermal delivery of drugs is still an underutilized delivery system in Europe, thus offering a great potential.
- Transdermal delivery may have different advantages over other delivery systems, including:
    - Avoids gastrointestinal (GI) drug absorption difficulties caused by GI pH, enzymatic activity and drug interactions with food, drink, and other orally administered drugs.
    - A substitute for other routes of administration (e.g. oral administration, intravenous injection) when that route is unsuitable, as with vomiting, swallowing problems, resistant children and diarrhea.
    - Avoids the first-pass effect, possibly avoiding the deactivation by digestive and liver enzymes.
    - Patient acceptability. Transdermal delivery is noninvasive, avoiding the inconvenience of parenteral therapy.
    - Ability to dissolve a wide range of medications with different chemical properties, making combination therapy with one transdermal cream possible.
    - Provides extended therapy with a single application, improving compliance.
    - Drug therapy may be terminated rapidly by removal of the application from the skin surface.[1]
- Ease of preparation; with Pentravan®, a transdermal cream can be compounded in three simple steps (see chapter “Method of preparation” on page 10).

For more information about transdermal delivery systems and their advantages, please see the article of L.V. Allen Jr. in appendix 1.

Advantages/USPs of Pentravan® vs. PLO and other transdermal bases

Compared to PLO, Pentravan® offers the following advantages:

- *Greater rate and extent of absorption*. An in vitro study published in the May/June 2012 edition of the IJPC shows that the Pentravan® formulation delivers 3.8 fold more ketoprofen than the PLO formulation (P=0.091). For testosterone the difference is smaller (P=0.2446), but the results do still demonstrate a 1.7-fold greater delivery from the Pentravan® formulation. Pentravan® will likely show similar delivery improvements with other topical NSAIDs, hormones and APIs.[3]
- *Patient friendly*
    - Vanishing cream base, not leaving a sticky residue.
    - No need to cover the area of application to ensure therapy effectiveness.
    - The cream is less greasy.
    - The cream almost has no smell, a slight odor of lecithin.
- *Ease of preparation*. With Pentravan®, a transdermal cream can be compounded in three simple steps (see chapter “Method of preparation” on page 10). For PLO, the method of preparation is more extensive. To prepare PLO, the oil and aqueous phase need to be mixed using a high-shear mixing method - for example, using two syringes, connected by a luer lock or by using an electronic pestle and mortar. Besides that, the aqueous phase needs to be cold (i.e. 0˚C), while the oil phase should be at room temperature.[2]

Compared to PLO and other alternatives, Pentravan® offers the following advantage:

- *Greater loading capacity* for APIs than alternatives. This makes it possible to compound creams with higher concentrations and more than one API when needed.[3]

The full article *"In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream"* (Lehman, P.A., Raney, S.G. IJPC, Vol. 16 (43). May/June 2012.) is included in appendix 2. In this article you will find two graphs depicting the results of the study in a visual way.

PRODUCT INFORMATION

Commented [VN1]: New product photo

Production

Fagron US will produce Pentravan® for the US, Australian and Brazilian market. Fagron Czech Republic will be responsible for the production of Czech and Poland. Herkel is responsible for the rest of Europe.

FAUS
E: info@fagron.us
T: +800 423 6967

FACZ
E: obchod@fagron.cz
T: +420 585 202 461 / +420 585 202 465

Herkel
E: info@herkel.nl
T: +31 (0)36-5211800

Packaging

Pentravan® is available in 500 g units; packed in 650 mL plastic jars with red screw lid and seal. A technical specification sheet can be found in appendix 3.

Label

The global template for the Pentravan® label is available, you can find these in the Fagron Label Directives.

Material safety data sheet

A material safety data sheet is available in 15 languages. An example, in English, can be found in appendix 4.

Certificate of analysis

A certificate of analysis is available in 4 languages. An example, in English, can be found in appendix 5.

How to order Pentravan®

Orders for 500 g jars with Pentravan® should be directed to Herkel. The transfer price for the 500 g jars is EUR 5.97 (ex works Herkel).

Samples

Upon request a quotation can be provided by Herkel for Pentravan® samples.

Pricing strategy

The pricing strategy for Europe has been determined:

- The transfer price for the 500 g jars Pentravan® is EUR 5.97 (ex works Herkel).
- The minimum sales price for the 500 g jars Pentravan® is EUR 27.50. Please note that is not allowed to sell the 500 g jars Pentravan® for a price below EUR 27.50.
- The minimum order quantity is 60.

Photography

Photography of a jar of Pentravan® is available online in the Fagron Brand Portal. Currently, there is a photograph available of a jar of Pentravan® and Pentravan® Plus. These photographs are also attached in appendix 6.

Please note that photographs showing the use of Pentravan® on body parts should be used with consideration. Suggested areas for application of Pentravan® are the abdomen, inner arms, and thighs. However, with certain therapies (e.g. pain management) Pentravan® can also be applied on other body parts. Photographs used in marketing materials should therapeutically be in line with the context.

Trademark status

Pentravan® has a trademark in the United States of America and the Benelux. Fagron GMI is in the process of registering Pentravan® as a trademark for Europe in the beginning of 2017.

Fagron Group BV - Lichtenauerlaan 182, 3062 ME Rotterdam - The Netherlands - Tel. +31 (0)88 33 11 288 - Fax +31 (0)88 33 11 210
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TECHNICAL AND PHARMACEUTICAL INFORMATION

Technical data sheet

Please see appendix 7 for the technical data sheet of Pentravan®.

Composition Pentravan®

Purified water
Isopropyl myristate
Lecithin (soy)
BHT
Simethicone
Urea
Potassium sorbate
Polyoxyl 40 stearate
EDTA
Cetyl alcohol
Stearyl alcohol
Stearyl acid
Glyceryl monostearate
Sorbic acid
Benzoic acid
Carbomer 980 NF Polymer
Buffered with hydrochloric acid 37%

Description: stiff, yellow cream; slight odor of lecithin.
pH 4.0 - 5.5.

Note: information about the composition of Pentravan® is intended only for internal use and should not be shared with third parties.

Emulsifying agents

Emulsifying agents present in Pentravan® are polyoxyl 40 stearate, cetyl alcohol, stearyl alcohol and stearic acid.

Storage conditions

Pentravan® should be stored in the original jar at room temperature (15˚C - 25˚C). Conducted stability studies show stability of Pentravan® under various testing conditions. Therefore no labelling statement concerning storage conditions is required.

Microbiology

A microbial test shows that Pentravan® does not grow microbes during storage.

Shelf life of Pentravan® (unopened)

Stability studies show that an unopened jar of Pentravan® (as a ready-to-use base) remains stable and suitable for use for three years after the date of manufacture. For information and results of the stability study, please see appendix 8.

Shelf life of Pentravan® (after opening)

The results of the antimicrobial effectiveness testing conducted by Fagron US show a one year shelf life of a jar Pentravan® (as a ready-to-use base) after opening. For information and results of the stability study, please see appendix 9.

APIs suitable for transdermal delivery in Pentravan®

An ideal API for transdermal delivery is:

- A potent chemical with a daily dose of a few milligrams.
- A small molecule; the molecular weight of the API molecules used should be between 100 to 800 u, with a mass <400 u considered optimal.
- One that has a high lipid solubility and reasonable water solubility, or one that has solubility in a solvent which is miscible with the Pentravan®. Examples of solvents that are miscible with Pentravan® can be found in the table included in appendix 10.
- Non-irritating and non-sensitising to the skin.[2]

To be suitable for transdermal delivery in Pentravan®, an API does not have to meet all the criteria mentioned above; there is a variety of successful formulations for transdermal drug delivery systems with APIs that do not meet all these criteria.[2]

Analgesics, NSAIDs, antiemetics, vasodilators, and hormones are most often used with Pentravan®. Examples of APIs that could be used with Pentravan® are listed in appendix 10.

APIs to avoid delivering in Pentravan®

- *Antibiotics:* molecule is too large to pass completely through the skin. The risk of resistance to the antibiotic is significant. In the US, transdermal delivery of antibiotic for systemic absorption is not recommended for this reason.
- *Prodrugs:* because of the route of administration, no drug passes the gut wall and very little arrives at the liver. Note: if transdermal delivery of a prodrug is requested

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to meet a patient specific need, suggested starting doses are half the oral dose if the drug is cleared by the liver and two times oral dose if drug is activated by the liver. Blood levels should be monitored. Veterinary patients have benefited from transdermal administration of prodrugs in some cases.

- *Antipsychotics:* in most cases the molecule is too large to pass the skin completely and reach the bloodstream. In addition, good therapy with these drugs requires steady-state blood level maintenance of the drug. Absorption through the skin may be erratic, making steady-state difficult to achieve. Transdermal administration has been attempted and evaluated. This is best accomplished with patients already showing good response to the drug.

Method of preparation

In general, the method of preparation can be described in the following three steps:

- *Step 1*: calculate, weigh and measure the APIs.
- *Step 2*: prepare APIs for inclusion into Pentravan®. Material(s) should be in the form of a smooth, non-gritty, homogenous paste before addition to Pentravan®. Reduce all powders to uniform, fine consistency with a ceramic mortar and pestle, then triturate with a suitable solvent to make a paste. A list of suggested solvents can be found in appendix 10.
- *Step 3*: combine the active ingredients and excipients with Pentravan® using geometric dilution techniques.

All these steps may be accomplished using an ointment slab, a mortar and pestle, a mechanical mixing device, or ointment mill.

Dispensing strategies

The applied dispensing procedure is defined by the accuracy of dosing that is required. For example, hormone doses are individualized per patient and should be dosed with high accuracy. A single dose may be dispensed in amounts ranging from 0.1 g to 1 g of Pentravan®. In contrast, NSAIDS and antiemetics are often prescribed to be given "as needed". The dose of these drugs is usually dispensed in 1 g of Pentravan®. Examples of dispensing systems are listed below.

<u>Ointment tube</u>
Instructions for a "visual" clue to the amount needed per application may be given to the patient. For example an amount the size of a pea approximates one dose. This method should not be used for APIs that need precise dosing (e.g. hormones).

<u>Unit dose mechanical dispenses</u>

- *AccuTenth dosing syringe*: designed to dispense 0.1 mL of a cream or gel. There is an audible, visual and tactile click registration for user recognition. This is an excellent device for dosing APIs that require precise dosing. A document with instructions how to use the AccuTenth dosing syringe can be found in appendix 11.
- *Airless Pump dispenser*: 0.5 g per actuation.
- *Oval metered pump dispenser*: approximately 1 g per actuation (dose varies from 0.800 g to 1.200 g).

- *Topi-Click dispenser:* dispenses 0.25 g per actuation. Topi-Click is a metering dispenser for topical creams or gels. After dispensing, the cream can be applied by rubbing the applicator pad to the area of skin. There is an audible, visual and tactile click registration for user recognition. In appendix 12 you will find a document with instructions how to use the Topi-Click dispenser.

EMP (electronic mortar and pestle) jar
Dosing occurs on "visual" clue as mentioned above for ointment tubes. Other products related to this jar are:

- Varionozzle insert: an insert for the jar to make it possible to load oral syringes for unit dose.
- Exact-Dose attachment: this unique and patient-friendly dosing system is designed to attach directly to an Unguator jar to provide accurate and reproducible 0.5 mL/gm doses of creams, ointments, and gels for transdermal or topical delivery with no need to transfer the preparation to a different container. This closed system also eliminates loading individual topical syringes.

A document with pictures of these dispensing systems and information about purchase prices and sales prices applied by Fagron US can be found in appendix 13.

For questions about the dispensing systems mentioned above, please contact Fagron US. These dispensing systems can be ordered at Fagron US, but this may not be desirable due to the costs for shipping and import.

Application route

Topical (cream).

Patient groups

Suitable for all patient groups.

Adverse reactions

None recorded, possible.

What the patient needs to know

Important information the pharmacist should provide the patient can be found in the article of L.V. Allen Jr. mentioned before (see appendix 1). The most important information is that application should be to clean, dry skin and not to oily, irritated, inflamed, broken, or callused skin. Rotating locations is important to allow the skin to regain its normal permeability and to prevent skin irritation. Skin sites may be reused after one week. Suggested areas are the abdomen, inner arms, and thighs. Application of the transdermal cream directly on the site of pain is also possible. Hands should be washed after applying the cream. The patient should not get the medication in his or her eyes or mouth.[1]

MARKETING

Marketing text

Commented [VN2]: No new marketing texts have been developed..

The following Pentravan® marketing text can be used for different marketing tools (e.g. newsletters, flyers, and website) and is created in two versions. Version A is intended for use in countries where prescribers and pharmacist are familiar with PLO. Version B is more suitable for use in countries where prescribers and pharmacists are not/less familiar with PLO and transdermal drug delivery.

Version A

Pentravan®
*'**Pen**e**tra**tion enhancing **Van**ishing Cream'*

Pentravan® is an oil-in-water emulsion base with a liposomal matrix for transdermal delivery of drugs. It uses the same penetration enhancing ingredients as those used in PLO formulations, but without the sticky residue. Pentravan® is a fragrance free, vanishing cream, providing a cosmetically elegant skin feel.

An in vitro absorption study with different APIs shows that Pentravan® delivers **more** drug in a **shorter** amount of time than PLO.*

Comparing permeation of drugs in Pentravan® vs. PLO:

- *The API in Pentravan® reached peak permeation faster.*
- *The amount of drug in Pentravan® that is absorbed is pharmacologically higher.*
- *Ketoprofen in Pentravan® shows a 3.8 higher absorption than in PLO.*
- *Testosterone in Pentravan® shows a 1.7 higher absorption than in PLO.*

Benefits of Pentravan®
- *Proven effectiveness and reproducibility of transdermal drug delivery.*
- *Ready-to-use base, allowing an easy three step preparation of transdermal creams. Less mixing and less preparation time.*
- *Better skin feel for enhanced patient satisfaction and compliance.*
- *Minimal odor. Fragrance-free formula.*
- *A noninvasive, patient-friendly alternative for other routes of administration.*
- *Versatile. Pentravan® can be used with a broad variety of APIs.*

Individualized, patient friendly transdermal creams are easily prepared in three steps with Pentravan®.

Method of preparation
1. *Calculate, weigh and measure the APIs.*
2. *Prepare API(s) for inclusion into Pentravan®. Material(s) should be in the form of a smooth, non-gritty, homogenous paste before addition to Pentravan®. Reduce all powders to uniform, fine consistency with a ceramic mortar and pestle, then triturate with a suitable solvent (e.g. water) to make a non-gritty, homogenous paste.*
3. *Combine the API(s) and excipients with Pentravan® using geometric dilution techniques.*

*Visit our website (*insert address webpage*) to see how easy it is to compound a transdermal cream with Pentravan®.*

With Pentravan® Fagron provides a perfectly unique and innovative vehicle in the fundamental compounding service.

Please contact us if you want to know more about Pentravan® or our other compounding vehicles.

* Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

Version B

Pentravan®
*'**Pen**e**tra**tion enhancing **Van**ishing Cream'*

Individualized, patient friendly transdermal creams are easily prepared in three steps with Pentravan®.

Pentravan® is an oil-in-water emulsion base with a liposomal matrix for transdermal delivery of drugs. It uses penetration enhancing ingredients to ensure effective and

reproducible transdermal delivery of drugs. Pentravan® is a fragrance free, vanishing cream, providing a cosmetically elegant skin feel.

Benefits of Pentravan®
- *Proven effectiveness and reproducibility of transdermal drug delivery.*
- *Ready-to-use base, allowing an easy three step preparation of transdermal creams. Less mixing and less preparation time.*
- *Better skin feel for enhanced patient satisfaction and compliance. A vanishing cream that requires no covering of the treated area.*
- *Minimal odor. Fragrance-free formula.*
- *A noninvasive, patient-friendly alternative for other routes of administration.*
- *Versatile. Pentravan® can be used with a broad variety of APIs.*

Individualized, patient friendly transdermal creams are easily prepared in three steps with Pentravan®.

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3. *Combine the API(s) and excipients with Pentravan® using geometric dilution techniques.*

*Visit our website (*insert address webpage*) to see how easy it is to compound a transdermal cream with Pentravan®.*

With Pentravan® Fagron provides a perfectly unique and innovative vehicle in the fundamental compounding service.

Please contact us if you want to know more about Pentravan® or our other compounding vehicles.

Background information on transdermal drug delivery

Background information on transdermal drug delivery can be found in appendix 14. This text can be used for creating your marketing tools.

Formulations

Fagron US has developed formulations based on Pentravan® which are based on extrapolation of PLO data. These formulations can be found in appendix 15.

Pain management

Pain management is an area in which transdermal creams have a significant added value. We have dedicated a full section to the application of transdermal creams in pain management, including formulations. This material will support you in introducing

Pentravan®, please see it in appendix 16. In 2016, Fagron developed a new pain vehicle that will be launched very soon. In the therapeutic area of pain management this vehicle is superior compared to Pentravan®.

Marketing photography

Photographs that can be used for the introduction of Pentravan® can be found in the Fagron Brand Portal. These photograph are also attached in appendix 6. Also attached in appendix 6 are high resolution versions of the graphs originating from the in vitro absorption study that was conducted to asses the delivery of ketoprofen and testosterone from PLO and Pentravan®. These graphs are extracted from the article *"In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream"* (Lehman, P.A., Raney, S.G. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.) The full article is attached in appendix 2.

When using the graphs in your marketing material please always make a reference note to this article. The following notation can be used:

> Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

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Demonstration videos

Fagron demonstration videos showing Pentravan® and PLO and the method of preparation are currently being developed. Also Fagron demonstration videos on the before mentioned dispensing systems will be developed. These videos can be used for marketing and educational purposes. You will be updated about the availability of these videos.

Commented [VN3]: These videos were never created?

Fagron Academy

A doctor and pharmacist are involved in the lectures and courses of Fagron Academy.

Dr. Hugo da Silva Maia Jr. is a Brazilian doctor who is specialized in bioidentical hormone replacement therapy (BHRT) for women in the phase of menopause. He has given lectures on request for Fagron US and Fagron Brazil on this subject. During these occasions we have had Reginalda Russo, a pharmacist from Fagron Brazil, join him to complement his lecture with information about Pentravan® and transdermal delivery of drugs.

Dr. Hugo da Silva Maia Jr. has been giving a broad range of lectures and courses in different countries. He has been a member of different medical associations and he has participated in a variety of research projects. For the curriculum vitae of Dr. Hugo da Silva Maia Jr. please see appendix 17.

Reginalda Russo is a Brazilian pharmacist working for Fagron Brazil. Since 1989, she has been working for compounding pharmacies in Brazil. During the past fourteen years, she has been extensively involved in sharing knowledge about BHRT.

Reginalda is the first pharmacist in Brazil that started talking about BHRT. She has created lectures and courses on this subject for pharmacists as well as prescribers. The second edition from the book she published on BHRT in 2009 has recently been printed. Besides working at the innovation department of Fagron Brazil, she is also a member of the Anfarmag, the Brazilian Compounding Pharmacies Association, in which she is a member of the technical committee.

When there is sufficient interest from the European Fagron countries, lectures intended to inform and educate your organization and your sales team on BHRT, Pentravan® and transdermal delivery of drugs could be organized. This could also be done through OCs.

There is also the possibility to get lectures organized in your country intended for prescribers and pharmacists.

IN VITRO ABSORPTION STUDY

Carried out by
Paul A. Lehman, MSc. and Sam G. Raney, PhD (Cetero Research, Fargo, United States).

Goal
Asses the difference in in vitro delivery of ketoprofen and testosterone from two different base formulations (PLO vs. Pentravan®).

Method
Franz Diffusion Cell, trunk skin of 3 ex vivo donors, receptor solution collection over 48 hours.

Test APIs
Testosterone (hormone) and ketoprofen (NSAID).

Summary results
Both ketoprofen and testosterone show *in vitro* penetration into and through the *ex vivo* skin. The penetration profile of ketoprofen is similar in both tested formulations. The penetration profile of testosterone varies somewhat between the tested formulations. With ketoprofen a statistically significant difference is assessed. The Pentravan® formulation delivers 3.8 fold more ketoprofen than the PLO formulation (P=0.091). For testosterone the difference was smaller (P=0.2446), but the results do still demonstrate a 1.7 fold greater delivery from the Pentravan® formulation. Pentravan® will likely show similar delivery improvements with other topical NSAIDs, hormones and APIs.

The results of this study are published on the IJPC website on March 23 and in the May/June printed edition of the IJPC. The full article *"In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream"* (Lehman, P.A., Raney, S.G. IJPC, Vol. 16 (43). May/June 2012.) is included in appendix 2. In this article you will find two graphs depicting the results of the study in a visual way.

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Although this study only addresses the rate and extent of drug delivery for two popular formulations for topically applied compounding preparations, it is reasonable to anticipate that, relatively to the PLO, Pentravan® might likely provide similarly enhanced delivery and performance with most other topically applied NSAIDs and hormones in a related chemical class to ketoprofen and testosterone. Similar results may also be expected from other APIs used in PLO based formulations.

Evaluation of Pentravan®, Pentravan® Plus, Phytobase®, Lipovan® and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital.

Carried out by
Kirilov et al.

Goal
The objective of the study by Kirilov et al. was to investigate the percutaneous absorption of enrofloxacin from two base formulations, Pentravan® cream and LMOG organogel.

Method
The two formulations were tested on pig ear skin and the percutaneous permeation was measured and compared using Franz diffusion cells.

Test APIs
Enrofloxacin

Enrofloxacin is an antibiotic used in the treatment of animals that suffer from respiratory- and digestive bacterial infections. The flux values were 0.35 mg/cm²/h for Pentravan® and 1.22 mg/cm²/h for LMOG Organogel, corresponding to 7.9 % and 29.3 % of enrofloxacin absorbed after 120 h by these formulations. The lag time (reaction) of Pentravan® and organogel were 6.32 and 0.015 h. The absorption time to reach the required antibiotic concentration of enrofloxacin (2 mg/ml) in the receptor was 60 h with Pentravan® and 30 h with the organogel, suggesting more effective treatment by LMOG.
Enrofloxacin contained in organogel could be absorbed through pig ear skin 3.7 times greater than that in Pentravan®. This study demonstrates the perspective of organogel formulations as potential drug delivery systems and the improvements that need to be made for the Pentravan® formulation. Future studies should focus on the systemic effects of both formulations.

Find the study here

Evaluation of Pentravan®, Pentravan® Plus, Phytobase®, Lipovan® and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital.

Carried out by
Bourdon et al.

Goal
Five commercial ready-to-use transdermal vehicles (Phytobase®, Lipovan®, Pentravan®, Pentravan® Plus, Pluronic Lecithin Organogel (PLO)) were evaluated for the compounding of three antiemetic drugs (ondansetron, dexamethasone and aprepitant).

Method
Diffusion experiments were performed by using synthetic membranes and pig ear epidermis on Fransz-type diffusion cells.

Test APIs
Testosterone (hormone) and ketoprofen (NSAID).

The drugs studied are regularly used to treat chemotherapy-induced nausea and vomiting in oncology patients. The release and permeation was greatest for ondansetron, then dexamethasone and aprepitant was discarded because permeability was too low to allow transdermal administration. The most efficient vehicle was Pentravan® Plus in inducing diffusion of ondansetron and dexamethasone across the skin, also the preparation of Pentravan® Plus was very easy and efficient, therefore favored by the authors.
At this stage, the permeation of the tested APIs in Pentravan® Plus does not allow transdermal administration in adults, although the initial results look promising. The university of Lille will perform future studies with a focus on optimizing the therapeutic effect of ondansetron and dexamethasone in Pentravan® Plus by adding various penetration enhancers.

Find the study here

Transdermal Oxandrolone: Ex Vivo Percutaneous Absorption Study

Carried out by
Polonini et al.

Goal
The objective of this study was to evaluate the permeability of oxandrolone in human skin *ex vivo* for possible future determination of the transdermal route as an alternative to oral treatments.

Method
Franz diffusion cells coupled with freshly excised human skin were used.

Test API
Oxandrolone is a synthetic testosterone analogue FDA approved for use as oral therapy for weight gain in patients with a weight loss as a consequence of for example major surgery, chronic infection, or severe trauma.

The drug release kinetics were determined to predict the efficiency of this alternative route for the drug. 236 µg (86.7%, of the applied dose) of the product did not permeate through the skin due to the barrier function of the stratum corneum; 21.6% reached the receptor medium, and the remaining 4.3% were within viable layers of the skin.

The total amount of drug able to induce an effect is the sum of the drug quantified within remained skin and the receptor medium. In this case, a total of 247.6µg of oxandrolone (25.9% of the applied dose) would be able to permeate through a non-damaged skin.

Transdermal oxandrolone could be a viable alternative for the traditional oral form, once clinical studies are conducted to prove this hypothesis.

Find the study here.

Transdermal formulations containing human sexual steroids: development and validation of methods an in vitro drug release.

Carried out by
Polonini et al

Goal
The in vitro release of bioidentical hormones in four different liposomal transdermal emulsions was investigated.

Method
Novel high-performance liquid chromatography methods were developed and validated to determine the in vitro release.

Test APIs
Testosterone, progesterone, estradiol, estriol

The methods were suitable for our intended goal, and the emulsions effective as transporting candidates for the efficient release of hormones in the transdermal delivery of human sexual steroids. In conclusion validated HPLC methods were successfully developed that are facile and eco-friendly for transdermal emulsions containing human sexual steroids (testosterone, progesterone, estradiol, or estradiol and estriol).
Furthermore, the physiological receptor media for these formulations were successfully determined for *in vitro* drug release. Moreover, drug release measurements were performed to obtain optimal release rates of formulations. From this, we discovered that the vehicle

Pentravan® exhibited high releases rates of incorporated hormones, proving to be an optimal option for transdermal route.

Find the study here.

Evaluation of percutaneous absorption performance for human female sexual steroids into Pentravan cream.

Carried out by
Polonini et al.

Goal
The purpose of the study was to evaluate the transdermal delivery of Pentravan®. The permeation for progesterone, estradiol, and estriol in separate formulations, as well as a combination of estradiol + estriol (Biest), was evaluated regarding the compounding process and the potential biological application.

Method
A female human skin model was used to predict the permeation and the retention of the APIs in every skin layer.

Test APIs
Progesterone, estradiol, estriol, Biest.

Progesterone was the drug with the highest permeation (37.02 mcg/cm² at the end of the experiment). Estradiol and estriol in Biest had permeations approximately 4-fold lower (9.44 mcg/cm² for estradiol-Biest and 14.02 mcg/cm² for estriol-Biest), and the profiles of estradiol in Eemuls and in Biest were almost the same (9.46 mcg/cm² for Eemuls). All permeations followed pseudofirst order kinetics.

For progesterone, using the percentage of permeation by dose, one can assume that a patient using the 1g emulsion dose released by the pump containing 50 mg of progesterone will have a release of 38.4 mg of progesterone into the bloodstream, gradually and continuously for 48 hours. The results indicate that Pentravan® was able to provide percutaneous absorption rates compatible with and higher than clinical treatment needs.
According to the results, human female sexual hormones incorporated in Pentravan oil-in-water vanishing cream base and applied topically are expected to have biological activity systemically with good efficacy due to their permeation through human skin. Care has to be taken regarding the quantity of emulsion used to avoid patient overdose, in the study high doses were applied.

Find the study here.

QUESTIONS AND ADDITIONAL INFORMATION

All questions you might have after reading this Pentravan® global asset kit can be addressed to the global marketing by e-mail: globalinnovation@fagron.com or phone: +31 88 33 11 283.

When we get a repeated request for a certain time of information we ensure that this information is shared with all Fagron countries.

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References

1 Allen, L.V. Jr. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding;* 15 (4). July/August 2011.

2 Murdan, S. A review of pluronic lecithin organogel as a topical and transdermal drug delivery system. *Hospital Pharmacist;* 12. July/August 2005.

3 Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

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APPENDIX 1

Article L.V. Allen, Jr. "Transdermals: the skin as a part of a drug delivery system"

APPENDIX 2

Article P.A. Lehman, S.G. Raney "In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic Lecithin organogel vs. Pentravan® cream"

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APPENDIX 3

Technical specification sheet CurTec KHM Packaging 650 mL Packo with red screw lid and seal

APPENDIX 4

Example of a material safety data sheet

APPENDIX 5

Example of a certificate of analysis

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APPENDIX 6

Marketing photography

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APPENDIX 7

Pentravan® technical data sheet

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APPENDIX 8

Pentravan® stability study (unopened)

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APPENDIX 9

Pentravan® stability study (opened)

APPENDIX 10

List of APIs commonly included in Pentravan®

Chemical Name	Usual Concentration	Suggested Solvent
Acetaminophen (paracetamol)	10%	ethanol
Amitripyline HCl	2%	water
Cyclizine	at oral dose	ethanol
Cyclobenzaprine	0.2% to 2%	water
Carbamazepine	2%	propylene glycol, ethanol
Clonidine	0.2%	water
Dexamethasone sodium Ph.	2% to 5%	water
Diclofenac Sodium	1% to 5%	propylene glycol
Diphenhydramine HCl	at oral dose	water
Estrogen	at oral dose	oil, ethanol
Gabapentin	2% to 6%	water
Haloperidol	at oral dose	propylene glycol
Ibuprofen	20%	ethanol
Indomethacin	2% to 4%	ethanol
Ketamine HCl	2% to 10% (5% standard)	water
Ketoprofen	5% to 20%	ethoxy diglycol, ethanol 200 pr
Ketorolac	2%	ethanol
Lidocaine	2% to 10%	ethanol
Lidocaine HCl	2% to 10%	water
Lorazepam	at oral dose	propylene glycol
Metoclopramide	at oral dose	ethanol
Morphine sulfate	10%	water
Naproxen	10%	ethanol
Nifedipine	2%	ethanol
Piroxicam	1%	ethanol
Progesterone	up to 200 mg/dose	oil, ethanol
Promethazine HCl	at oral dose	water
Sildenafil	at oral dose	ethanol
Tetracaine HCl	2% to 10%	water
Tetracaine	2% to 10%	ethanol
Testosterone	up to 2%	oil, ethanol

APPENDIX 11
AccuTenth dosing system instructions

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APPENDIX 12

Topi-Click dispenser instructions

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APPENDIX 13

Pictures of several dispensing systems suitable for Pentravan® based transdermal creams

Ointment tube
Item# 801782
4 oz laminated tube
Purchase price: 0.30 USD
Sales price: 0.95 USD

Metal tube
Item# 802915
4 oz metal tube
Purchase price: 0.20 USD
Sales price: 1.20 USD

AccuTenth dosing syringe
Item# 805083
35 g container
Purchase price: 3.70 USD
Sales price: 4.95 USD

Airless Pump dispenser
Item# 800178
100 g container
Purchase price: 0.85 USD
Sales price: 2.75 USD

Oval metered pump dispenser
Item# 802023
100 g container
Purchase price: 0.65 USD
Sales price: 2.85 USD

Topi-Click dispenser
Item# 805217 (pink, other colored tops available)
35 g container
Purchase price: 2.50 USD
Sales price: 3.75 USD

EMP jar
Item# 801834 (10 pack)
100 g container
Purchase price: 13.59 USD (10 pack)
Sales price: 22.00 USD (10 pack)

Varionozzle insert
Item# 801866 (50 pack)
Varionozzle 4 mm
Purchase price: 9.94 USD (50 pack)
Sales price: 12.85 USD (50 pack)

Exact- Dose attachment
Item# n/a
Exact-Dose attachment, fits all EMP jars
Purchase price: n/a
Previous sales price: 3.00 USD

(are currently in production; expected to be available by the end of summer, 2012. Updated information will be shared with you as soon as it becomes available).

Source: Fagron US

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APPENDIX 14
Background information on transdermal drug delivery

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TRANSDERMAL DRUG DELIVERY

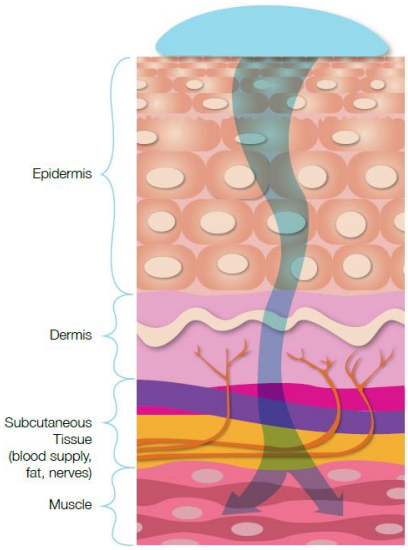
From pain relief gels through to nicotine patches, transdermal (through the skin) application is increasingly common.

While we tend to think of ourselves as 'waterproof' the reality is our skin is porous and certain substances are absorbed, not just into the skin but into the fat tissue beneath and the blood stream itself.

Transdermal delivery involves the passage of therapeutic quantities of drug substances through the skin and into the general circulation for systemic effects. Transdermal delivery of drugs is effective and used to treat many different conditions. Examples of drugs that are routinely used in transdermal delivery systems include: hormones, pain medications, nonsteroidal, anti-inflammatory drugs (NSAIDs), antinauseant medications, and many others.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY

- Avoids the first-pass effect of the liver
- Avoids gastrointestinal drug absorption difficulties
- Patient acceptability; transdermal delivery is noninvasive
- Provides extended therapy with a single application, improving compliance
- Ability to dissolve a wide range of medications with different chemical properties, making combination therapy with one transdermal cream possible
- A substitute for other routes of administration when needed
- Provides extended therapy with a single application, improving compliance
- Drug therapy may be terminated rapidly by removal of the application from the skin surface



HOW IT WORKS

Transdermal absorption of a drug results from direct penetration of the drug through the stratum corneum (SC). It is the outermost layer of the epidermis; a 10 to 15 µm thick layer of flat, partially desiccated, nonliving tissue. The lipid content is concentrated in the extracellular phase of the SC and forms a drug's major route of penetration. Once through the SC, the drug molecules pass the deeper epidermal tissues, into the dermis and finally will reach the vascularised dermal layer. It then becomes available for absorption in the general circulation.

COMPOUNDING TRANSDERMAL CREAMS

Pentravan® is a ready-to-use base for compounding transdermal creams in a quick and efficient way. With Pentravan® transdermal drug delivery systems can be "individualized" for your patient by changing the drugs your patient needs, their concentrations, and the formulation. For more information about Pentravan® please contacts us.

APPENDIX 15

Example formulations with Pentravan®

ABHR in Pentravan®

(metoclopramide 1 mg, diphenhydramine hcl 25 mg, haloperidol 1 mg, lorazepam 0.5 mg)
Calculated to make 100 g

INGREDIENTS

metoclopramide HCl USP	0.100 g
lorazepam	0.050 g
diphenhydramine HCl USP	2.500 g
haloperidol USP	0.100 g
ethoxy diglycol	q.s. to wet powders
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powders, if necessary with the use of a mortar and pestle.
- Dissolve the metoclopramide, diphenhydramine HCl, haloperidol and lorazepam using a small amount of ethoxy diglycol or ethanol to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

Notes

Metoclopramide is soluble 1.9 g/100 mL of ethanol. Lorazepam is soluble 14 mg/mL in ethanol, 16 mg/mL propylene glycol. Diphenhydramine HCl is soluble 1:1 in water and 1:2 in ethanol. Haloperidol is solution 1.4 mg/100 mL in water, freely soluble in acetone. Ethoxy diglycol has been found to be a suitable solvent for the combination of these active ingredients.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 7 (3): p 183.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

Moon, Richard b, PharmD, RPh,. ABHR Gel in the Treatment of Nausea and Vomiting in the Hospice Patient. *International Journal of Pharmaceutical Compounding* v10,#2,pp95-98.

AMITRIPTYLINE 2% in Pentravan®

Calculated to make 100 g

INGREDIENTS

amitriptyline HCl	2.000 g
water	q.s.
Versigel®	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the amitriptyline HCl, if necessary with the use of a mortar and pestle.
- Levigate the amitriptyline HCl with an appropriate amount of purified water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to reach approximately 90% of final volume, stirring well after each addition of Pentravan®.
- Evaluate viscosity of the preparation and add Versigel® as needed with mixing to obtain desired thickness.
- Add sufficient Pentravan® to bring to final weight.
- Package and label.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Amitriptyline HCl is freely soluble in water. The Zwitter-ionic nature of amitriptyline HCl may overwhelm the Pentravan® emulsion and thin the preparation. In this preparation, Versigel® - a sodium polyacrylate thickener - seeks out the water in the vanishing cream and forms a gel matrix within the cream, thus thickening it. If needed, Versigel® may be added drop-wise to thicken the preparation to its original viscosity. Versigel® should be added before final weight is reached so that the concentration of active ingredient is not reduced.

Versigel® (Fagron US) is a thickening, dispersed into a vegetable oil, ready-to-use liquid polymer that may be used over a wide pH range and immediately forms a gel on contact with water. Versigel® can be ordered at Fagron US and is available in volumes of 100 g and 500 g at a transfer price of USD 7.75 (ex works Fagron US; sales price USD 16.48) and USD 26.25 (ex works Fagron US; sales price USD 66.95), respectively. When there is sufficient interest for this product in Europe, distribution may be transferred to Europe. For orders and questions about Versigel® please contact Fagron US.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 4 (2): p 132.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

CARBEMAZEPINE 5% in Pentravan®

Calculated to make 100 g

INGREDIENTS

carbemazepine USP	5.000 g
ethanol	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powder, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of ethanol to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

Notes

Carbemazepine is practically insoluble in water, but soluble in ethanol.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 15 (2): p 157.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

FENTANYL 12.5 µg/0.1 g in Pentravan®

Calculated to make 10 g

INGREDIENTS

fentanyl *citrate*	1.963 mg
water	q.s.
Pentravan®	q.s. ad 10.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powder, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of water to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS

Accutenth® syringe.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general the cream should be applied as needed. Areas for application are the area of pain, or non-hairy, thin-skinned area. The inner wrist or ankle are good sites as the capillary bed is just below the skin in these areas. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Fentanyl citrate is soluble 1 g in 40 mL in water. 100 µg fentanyl is equivalent to 157 µg fentanyl citrate. Fentanyl citrate preparations should be protected from exposure to light and air.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 6 (1): p 45.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

GABAPENTIN 6% in Pentravan®

Calculated to make 100 g

INGREDIENTS

gabapentin	6.000 g
water	q.s.
Versigel®	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the gabapentin, if necessary with the use of a mortar and pestle.
- Levigate the gabapentin with an appropriate amount of purified water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to reach approximately 90% of final volume, stirring well after each addition of Pentravan®.
- Evaluate viscosity of the preparation and add Versigel® as needed with mixing to obtain desired thickness.
- Add sufficient Pentravan® to bring to final weight.
- Package and label.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

The Zwitter-ionic nature of gapabentin may overwhelm the Pentravan® emulsion and thin the preparation. In this preparation, Versigel® - a sodium polyacrylate thickener - seeks out the water in the vanishing cream and forms a gel matrix within the cream, thus thickening it. If needed, Versigel® may be added drop-wise to thicken the preparation to its original viscosity. Versigel® should be added before final weight is reached so that the concentration of active ingredient is not reduced.

Versigel® (Fagron US) is a thickening, dispersed into a vegetable oil, ready-to-use liquid polymer that may be used over a wide pH range and immediately forms a gel on contact with water. Versigel® can be ordered at Fagron US and is available in volumes of 100 g and 500 g at a transfer price of USD 7.75 (ex works Fagron US; sales price USD 16.48) and USD 26.25 (ex works Fagron US; sales price USD 66.95), respectively. When there is sufficient interest for this product in Europe, distribution may be transferred to Europe. For orders and questions about Versigel® please contact Fagron US.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 6 (1): p 42.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

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KETOPROFEN 10% in Pentravan®

Calculated to make 100 g

INGREDIENTS

ketoprofen USP	10.00 g
ethoxy diglycol	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the ketoprofen, if necessary with the use of a mortar and pestle.
- Levigate the ketoprofen with an appropriate amount of ethoxy diglycol to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Ketoprofen is practically insoluble in water but freely soluble in ethanol and ether. Although it is not listed in references, ethoxy diglycol has be found to be a more suitable solvent for this formulation because the amount needed to put ketoprofen into solution is far less than the listed solvents.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 5 (3): p 183.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

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KETOPROFEN 20% in Pentravan®

Calculated to make 100 g

INGREDIENTS

ketoprofen USP	20.00 g
ethoxy diglycol	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powder, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of ethoxy diglycol to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

Notes

Ketoprofen is practically insoluble in water but freely soluble in ethanol and ether. Although it is not listed in references, Ethoxy diglycol has be found to be a more suitable solvent for this formulation because the amount needed to put ketoprofen into solution is far less than the listed solvents.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 7 (3): p 183.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

MORPHINE SULFATE 5% in Pentravan®

Calculated to make 100 g

INGREDIENTS

morphine sulphate	5.000 g
water	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powder, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of water to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS

Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS

Use as prescribed. In general, 1 g should be applied, as needed. Areas for application are the area of pain, or non-hairy, thin-skinned area. The inner wrist or ankle are good sites as the capillary bed is just below the skin in these areas. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Morphine sulfate preparations should be protected from exposure to light and air.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 13 (3): p 244.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

PROGESTERONE 3% in Pentravan®

Calculated to make 100 g

INGREDIENTS

progesterone micronized	3.000 g
propylene glycol	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powder, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of propylene glycol to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

REFERENCES

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

GABAPENTIN 6% LIDOCAINE 4% in Pentravan®

Calculated to make 100 g

INGREDIENTS

gabapentin	6.000 g
lidocaine HCl USP	4.000 g
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powder, if necessary with the use of a mortar and pestle.
- Combine gabapentin and lidocaine HCl in appropriate unguator jar.
- Add Pentravan® to weight.
- Mix for 8 minutes at speed 5 using an unguator.
- (Package and) label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 6 (1): p 42.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

PROMETHAZINE HCl 5% in Pentravan®

Calculated to make 100 g

INGREDIENTS

promethazine HCl	5.000 g
water	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powders, if necessary with the use of a mortar and pestle.
- Levigate the powders with an appropriate amount of water to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water. Promethazine HCl is especially sensitive to light and air, professional judgement should be used to evaluate best BUD for patient.

Notes

Promethazine HCl is soluble 1 in 0.6 mL water; 1 g in 9 mL ethanol. Pentravan® contains sufficient water to solubilise the promethazine HCl. This preparation is often dispensed in amber syringes which contain only one, prefilled dose to safegaurd against overdose of small children for whom this preparation is often prescribed.

REFERENCES

Glisson, J.K., Wood, R.L., Kyle, P.B., Cleary, J.D. Bioavailability of promethazine in a topical pluronic lecithin organogel: a pilot study. *International Journal of Pharmaceutical Compounding*; 9 (3). July/August 2011. May/June 2005.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

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TESTOSTERONE 1% in Pentravan®

Calculated to make 100 g

INGREDIENTS

testosterone micronized USP	1.000 g
almond oil	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powders, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of almond oil to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

Notes

Testosterone USP is soluble in vegetable oils and in ethanol. This formulation is intended to provide systemic absorption of the drug, and for both male or female patients replacing hormone.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 5 (5): p 380.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

TETRACAINE HCL 2% in Pentravan®

Calculated to make 100 g

INGREDIENTS

tetracaine HCl	2.000 g
water	q.s.
Pentravan®	q.s. ad 100 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powders, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of water to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

Notes

Tetracaine HCl is freely soluble in water.

REFERENCES

Formulation: *International Journal of Pharmaceutical Compounding*; 15 (6): p 513.

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

KETAMINE 10% GABAPENTIN 6% CLONIDINE 0.2% in Pentravan®

Calculated to make 100 g

INGREDIENTS

ketamine HCl	10.00 g
clonidine	0.200 g
gabapentin	6.000 g
water	q.s.
Pentravan®	q.s. ad 100.00 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powders, if necessary with the use of a mortar and pestle.
- Levigate the powders with an appropriate amount of water to form a smoothe paste.
- Add sufficient Pentravan® to reach volume add the cream in small portions, stirring well after each addition.
- Package and Label

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

Notes

All APIs mentioned above are water soluble. The airless pump is suggested as a dispensing system for this cream. The airless pump provides 0.5 g per actuation of the pump. Patient should apply 2 pumps (1 g) per application.

REFERENCES

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

KETOPROFEN 5% GABAPENTIN 10% AMITRIPTYLINE HCl 2% LIDOCAINE HCl 5% in Pentravan®

Calculated to make 100g

INGREDIENTS

ketoprofen	5.000 g
gabapentin	10.00 g
amitriptyline HCl	2.000 g
lidocaine HCl	5.000 g
ethoxy diglycol or ethanol 200 proof	10-15mL
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powder, if necessary with the use of a mortar and pestle.
- Levigate the powders with an appropriate amount of ethoxydiglycol or ethanol 200 proof to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

REFERENCES

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

PROGESTERONE 6% TESTOSTERONE 2% in Pentravan®

Calculated to make 100 g

INGREDIENTS

progesterone micronized	6.00 g
testosterone micronized	2.00 g
ethyl alcohol 200 proof or propylene glycol	8.00 mL
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powders, if necessary with the use of a mortar and pestle.
- Levigate the powders with an appropriate amount of ethyl alcohol 200 proof or propylene glycol to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

REFERENCES

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

PROGESTERONE 20%
TESTOSTERONE 0,5%
PREGNENOLONE 5%
CHRYSIN 5% in Pentravan®

Calculated to make 30 g

INGREDIENTS

progesterone micronized	6.000 g
testosterone micronized	0.150 g
pregnenolone micronized	1.500 g
chrysin	1.500 g
almond oil, olive oil or grape seed oil	q.s.
Pentravan®	q.s. 30.00 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the powders, if necessary with the use of a mortar and pestle.
- Levigate the powder with an appropriate amount of almond oil, olive oil or grape seed oil to form a smoothe paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

STORAGE INSTRUCTIONS

Store at room temperature.

BEYOND USE DATE

Per USP monograph <795>, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels and lotions containing water.

Notes

This formulation is written for male patient. Chrysin is included to prevent estrafication of the testosterone.

REFERENCES

Allen, L.V. Jr.. Transdermals: the skin as part of a drug delivery system. *International Journal of Pharmaceutical Compounding*; 15 (4). July/August 2011.

Lehman, P.A., Raney, S.G. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International Journal of Pharmaceutical Compounding*; 16 (43). May/June 2012.

APPENDIX 16
Transdermal drug delivery in pain management

Fagron Group BV - Lichtenauerlaan 182, 3062 ME Rotterdam - The Netherlands - Tel. +31 (0)88 33 11 288 - Fax +31 (0)88 33 11 210
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TRANSDERMAL DRUG DELIVERY IN PAIN MANAGEMENT

The compounding pharmacist should be, and should be perceived as, a problem-solver. When administration, compliance, and efficacy are problematic for a particular patient, prescribers and patients should rely on the pharmacist to assist them with both knowledge and innovation to achieve the goal of overcoming the problem. Transdermal administration of medication has, in many cases, become one such innovation. While numerous clinical reports support this innovation, scientific data remains sparse, and the decision to utilize transdermal delivery remains a matter of professional judgment – meaning extrapolation and application of documented scientific information. Providing a solution to the problem is always the goal, and as with all innovation, some daring is required. So, we work together with other professionals to discern whether or not this innovative delivery system is appropriate. In the U.S., formulations for and clinical reports of efficacy have appeared in the literature over the course of the last decade.[1-5] These are generally written for the use of PLO as the transdermal vehicle. Fagron U.S. has documented improved efficacy by using Pentravan® as the transdermal vehicle, thus moving forward to the next level of innovation provided by this cream version of the PLO which is more cosmetically elegant and has better penetrating properties than the original PLO vehicle.[6]

For more detailed information about the advantages of Pentravan® compared to PLO and other transdermal bases, please see the Pentravan® global asset kit and the article by Lehman and Raney, 2012.[6] The Pentravan® global asset kit can be downloaded from the Fagron Brand Portal, accessible through #PentravanGlobalAssetKit.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY

Transdermal delivery represents an attractive alternative to other routes of administration of drugs. Transdermal delivery systems are popular because they have the following advantages over conventional drug delivery:

- They can avoid gastro-intestinal drug absorption difficulties caused by gastrointestinal PH, enzymatic activity and drug interactions with food, drink, and other orally administered drugs.
- They can substitute for oral administration of medication when that route is unsuitable, as in case of vomiting and diarrhoea.
- They avoid the first-pass effect of the liver that can prematurely metabolize drugs.
- They increase elimination half-life and establish high joint tissue: plasma concentration ratios resulting in prolonged therapeutic effect; thus improving compliance because less frequent dose administration is required.
- Drug therapy may be terminated rapidly by removal of the transdermal drug delivery systems from the surface of the skin.
- They are non-invasive, avoiding the inconvenience of parenteral therapy and increasing the patient's acceptability.
- They can be self-administered, allowing the patient to have self-control over the therapy.
- They allow combination therapy with one dosage; a wide range of drugs with different chemical properties can be included in the transdermal drug delivery system.
- Transdermal creams are easy to prepare, transdermal creams can be compounded in a few simple steps.
- The systems are generally inexpensive.[7-10]

More information about the advantages of transdermal drug delivery can be found in the Pentravan® global asset kit and the article by Allen, 2011.[11]

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MECHANISM OF TRANSDERMAL DRUG DELIVERY

The stratum corneum is the greatest barrier to transdermal transport and acts as a drug reservoir. Transdermal absorption of a drug generally results from direct penetration of the drug through the stratum corneum (SC), a 10 to 15 µm thick layer of flat, partially desiccated, nonliving tissue. After application on the skin, the drug molecules that are dispersed within the transdermal cream penetrate the SC through the intercellular channels. Once through the SC, drug molecules may pass through the deeper epidermal tissues and into the dermis. When the drug reaches the vascularized dermal layer, it becomes available for absorption into the systemic circulation.[11] As a result of this absorption process, there is a gradual release of the drug, which avoids peaks in plasma concentration and so adverse events are minimized.[7,11,12] A number of studies have shown that compounding bases for transdermal drug delivery systems have the unique capacity to deliver drugs across the epidermal barrier and deliver particular medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and local anaesthetics to a specific site.[13]

TRANSDERMAL DRUG DELIVERY IN PAIN MANAGEMENT

The management of pain is perhaps the most obvious area where transdermal administration of commonly used medications can be clinically effective in avoiding suboptimal outcomes. The primary benefit of transdermal administration is most often the avoidance of unpleasant adverse events that either reduce the quality of life, or worse, are at the root of non-compliance. Although oral NSAIDs are effective in relieving pain and reducing inflammation, their use show a high incidence of adverse events, notably dose-dependent gastro-intestinal disturbances such as nausea, vomiting, or dyspepsia. Furthermore, continued use of NSAIDs in particular can be harmful to body systems, because of accumulation in non-target organs. Prolonged high systemic drug concentrations after oral NSAID therapy may result in potentially serious adverse events such as gastrointestinal ulceration or bleeding, hypertension, and cardiovascular events, acute renal impairment, and hepatotoxicity.[13,14] The risk of such effects could be reduced by the use of topical formulations, which can deliver effective analgesic concentrations at the site of inflammation while minimizing systemic concentrations. Lower systemic concentrations after topical administration would also be expected to result in a lower risk of drug–drug interactions resulting from NSAID-mediated displacement of drugs binding to plasma proteins or alterations in drug concentrations due to induction or inhibition of cytochrome P450 enzymes. We also observe that invasive delivery systems for opioids are often uncomfortable for patients and stressful for caregivers. Patient acceptance and adherence to therapy may be better with topical formulations than with oral and invasive treatment because of the combination of improved tolerability and convenient dosing regimens.[13,14] Development of transdermal formulations has been based on this approach to overcoming these significant obstacles to efficacy and compliance.

NSAIDs are mainly used in the treatment of acute, nociceptive pain. Neuropathic pain however, responds poorly to treatment with NSAIDs and is difficult to treat successfully. Neuropathic pain is primarily the result of a neuropathic injury or modulation within the central nervous system and generally is a chronic, long-term disease process. Various types of drug therapy are used to treat neuropathic pain. While none are specifically designed for this purpose, there is some rationale for their use. Examples include: anticonvulsants, NSAIDs, narcotic analgesics, tricyclic antidepressants, ketamine, and clonidine.[15,16]

Due to the chronic nature of neuropathic pain, and undesirable side effects associated with most of the oral medications available for it, manufacturers and compounding pharmacists have worked on medications to treat neuropathic pain topically. Today, many compounded topical medications are used to treat chronic neuropathic pain effectively. The recent use of multifaceted regimens of topically applied medications has been anecdotally reported as being successful.[1-5,10,16,17]

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In many instances, pain and inflammation are localized to one part of the body. The bioavailability of topical NSAIDs has been reported to be generally less than 5% to 15%, while drug concentration at the site of administration can be 30-fold higher than with oral dose.[17] A plausible explanation might be that topical applied NSAIDs exert their pharmacological effects through localized accumulation at the application site rather than from systemic absorption.

TRIAD OF CARE: PATIENT, PRESCRIBER, PHARMACIST

Traditional dosage forms are prescribed by a doctor, physician's assistant or nurse practitioner and provided to the patient by the pharmacist. To successfully employ the innovation of transdermal drug delivery, the "triad of care" concept is imperative and it is best carried out through a partnership between prescriber and pharmacist. The experienced compounding pharmacist is essential to the physician, and the working partnership between these health-care professionals builds the practices of both groups while providing the best possible care for the patient. The triad works as follows.

Beginning with the patient, the prescriber identifies and assesses the need of the patient. A medication is chosen by the prescriber based on diagnosis, prognosis, their experience with traditional delivery systems and knowledge of the patient. What is the expected duration of treatment? For example, is pain medication required short-term post-injury or surgery, or will the patient require the medicine for many years? Has the patient shown a tendency for non-compliance? For example, is pain persisting due to non-adherence to the prescription protocol due to significant gastrointestinal distress that the patient associates with taking the medication? Is the pain transient or focused? Is it possible that an alternative dosage form would be more effective than traditional routes of administration? All these considerations constitute definition of the problem to be solved to improve outcomes.

Physicians and other prescribers need guidance from the pharmacist to meet the challenges presented in patients experiencing uncontrolled pain. The preponderance of clinical evidence regarding transdermal application of the medication should be seen as useful. This chapter includes references to scientific literature, but the combination of "proof" and "evidence" is the basis for professional judgment. The prescriber and pharmacist working together should determine a course of therapy including agreement on regular evaluation of the patient which may be used to adjust, or discontinue the chosen transdermal drug therapy. In truth, transdermal administration is most often supported by prescribers based on clinical response. A strong partnership between the professional prescribers and pharmacists builds confidence, innovation, and positive outcomes for patients. Formation of these bonds with prescribers results in repeat prescriptions for the pharmacy practice. Expansion of successful treatment regimens within the prescribers practice results in additional prescriptions. But the most important result is that more patients receive better relief from pain.

Finally, we return to the patient. What explanation is required to make them comfortable with the reason the transdermal route has been chosen and what instruction is required to ensure proper use of this unique dosage form? The first question may be answered most easily by explaining that the prescriber has chosen this medication to eliminate the unpleasant adverse events they have reported. Some patients can grasp the concept that by applying medication to the skin, their gut is avoided. Some patients cannot. Again, the pharmacist's role is imperative for compliance and time should be taken to explain as much as the patient can understand. Detailed instructions for use can often replace theoretical explanations.

An effective consult would include definition of the medication, instruction regarding use of the delivery device, and specific details of the method of application. For example: "Every gram of this cream contains one dose of your medication and you will be applying it to the site of your pain each 4 to 6 hours as needed. Your medication is packaged in a pump dispenser that releases one half of one gram each time you depress the top, so you will need to press the top twice to release one dose. Rub the cream into the skin until it disappears completely. Massaging the area for a full minute is recommended to ensure that all the cream containing medication vanishes into your skin. Wash hands after application so that any residue of the medication does not transfer to other persons through skin-

to-skin contact or to eyes or mouth." If a caregiver will be administering the medication these same instructions must be delivered to that individual.

Prescribing, compounding, and delivering transdermal medications represent the epitome of individualized patient care. It employs the knowledge and experience of health-care professionals to provide the best results for an individual patient. Clinical successes, and documentation of these successes, extend this possible benefit to more and more patients suffering from pain, which drives increased opportunities in the niche practice of compounding.

INNOVATIVE COMPOUNDING FOR PAIN MANAGEMENT

In the U.S., transdermal administration of medications grew primarily out of the need for innovation in pain management. Prescribers and pharmacists working together developed the transdermal drug system to address several issues such as non-compliance resulting from gastrointestinal adverse events and concerns about accumulation of drug in the liver and kidneys. In the 1990s, PLO became a frequently used base in which drugs can be incorporated for transdermal delivery. Collaborations between physicians and pharmacists led to the incorporation of a number of drugs into PLO and anecdotal evidence of its efficacy as a transdermal drug delivery vehicle.[18] In 2008, Pentravan®, a next-generation transdermal vehicle in this innovative delivery system was introduced. Prescribers and pharmacists requiring alternate dosage forms which avoid the issues inherent in pain management are using Pentravan® with extraordinary success.

Each of the formulations included in this chapter was originally written for use with PLO as the transdermal delivery vehicle. In a recent comparative study a greater rate and extent of absorption of two drugs was found from the Pentravan® formulation than from the PLO formulation.[6] Based on these results, the mentioned formulations have been adapted to utilize Pentravan® instead of PLO. It is important that pharmacists introducing transdermal drug delivery make themselves familiar with the information in this study. Please find this study listed in the references.

Download the Pentravan® global asset kit for more information about Pentravan®, its characteristics, advantages, technical information, compounding information and suggested formulations for various therapeutic indications. The Pentravan® global asset kit can be downloaded from the Fagron Brand Portal, accessible through #PentravanGlobalAssetKit.

KETOPROFEN

Ketoprofen was among the first drugs for which transdermal drug formulations were developed, and it remains the "strong-man" of most formulations used in managing pain. An NSAID like ketoprofen is usually given orally. Patients are evaluated for hypertension and cardiovascular health before receiving this drug and are also assessed for their individual potential for hepatotoxicity and renal impairment. In addition, gastrointestinal disturbances like nausea, vomiting, or dyspepsia as well as more potentially serious ulcerations or bleeding are concerns and are monitored during treatment with oral administration of ketoprofen. Transdermal administration of ketoprofen is expected to result in lower systemic absorption than in oral delivery, thus reducing these concerns. In transdermal delivery, ketoprofen is expected to act locally to relieve muscle pain. It has been found to be superior to diclofenac and piroxicam when applied three to four times daily to the site of pain[14] and formulations for 10%, 15%, and 20% are used widely in sports medicine.[19] A double-blind trial of transdermal ketoprofen returned reports that ketoprofen was comparable with oral celecoxib in relief of acute arthritic pain.[14] Case reports have shown benefits for patients suffering from neuropathic pain, post polio syndrome, fibromyalgia, and degenerative disc disease.[1-4]

Generally, ketoprofen is included in Pentravan® as a percentage of the volume dispensed. The most common formulations for treating muscle pain are written for 10% or 20% ketoprofen. When used to treat neuropathic pain, ketoprofen is often augmented with drugs more commonly associated with use in treating neuropathy. The pharmacist should keep this in mind when advising the prescriber, as the addition of another drug or drugs may contribute to further pain relief.

Tips and tricks

It is important to use ethoxy diglycol as solvent for ketoprofen in transdermal preparations. In order to dispense an elegant preparation, and to achieve best results, the active pharmaceutical ingredient should be in solution. Solubility of ketoprofen is approximately 1 to 1 in ethanol. In the following formulation written to make 100 grams of 10% ketoprofen in Pentravan®, this would require 10 mLs of ethanol. Adding that amount of liquid to Pentravan® will significantly thin the preparation and obviously ketoprofen 20% in 100 gram quantity even more so. Although references do not list ethoxy diglycol specifically as a solvent for ketoprofen, in fact, approximately 2 mLs of ethoxy diglycol will completely solubilise 10 grams of ketoprofen, thus keeping the Pentravan® in its original viscosity.

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KETOPROFEN 10% in Pentravan®
Calculated to make 100 g

INGREDIENTS

ketoprofen	10.00 g
ethoxy diglycol	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the ketoprofen, if necessary with the use of a mortar and pestle.
- Levigate the ketoprofen with an appropriate amount of ethoxy diglycol to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS
Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS
Store at room temperature.

BEYOND USE DATE
Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS
Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Ketoprofen is practically insoluble in water but freely soluble in ethanol and ether. Although it is not listed in references, ethoxy diglycol has be found to be a more suitable solvent for this formulation because the amount needed to put ketoprofen into solution is far less than the listed solvents.

GABAPENTIN

Anticonvulsants are traditionally given orally for treatment of seizures and can be an adjunct to treatment of neuropathic pain when other therapy does not adequately control the pain. It is thought that the mechanism of action for these agents is due to the stabilization of membranes. Success has been reported with some drugs in this class; however, gabapentin, an amino acid structurally related to the inhibitory neurotransmitter gamma-amino butyric acid (GABA), may be the best choice because blood counts are not necessary as with other anticonvulsant agents.[10,16,20] In addition, a review article from 2006 showed that gabapentin is effective in reducing postoperative pain, and that addition of the drug to an opioids regimen allows reduction of opioids use. The precise mechanism of analgesic action is unknown.[10]

While some systemic absorption of the drug is to be expected, transdermal administration of gabapentin results in lower systemic absorption than oral administration.[12] Transdermal administration of gabapentin should not be considered when treating seizures as blood level maintenance may not be reliable. However, in the treatment of neuropathy, especially diabetic neuropathy of the feet, clinical evidence supports transdermal administration of gabapentin.[17] In addition, because administration of gabapentin is usually long-term, transdermal administration solves the problem of dangerous accumulation of the drug. In addition, gastrointestinal distress, perhaps the most common and severe adverse events of continued oral administration, is avoided.[21]

Generally, gabapentin is included in Pentravan® as a percentage of the volume dispensed. Clinical reports are based on formulations containing 2%, 6% or 10% gabapentin applied directly to the site of pain. Gabapentin is often combined with ketoprofen, another NSAID, or a drug commonly used to treat neuropathy, muscle or nerve pain by oral administration, e.g. amitriptyline. Various formulations and case reports describing the effectiveness of transdermal systems with gabapentin have been published.[1-4,10,15,17,21] The pharmacist should keep this in mind when advising the prescriber since the addition of another drug or drugs to the gabapentin may contribute to improved pain relief.

Tips and tricks

The Zwitter-ionic nature of gabapentin may overwhelm the Pentravan® emulsion and thin the preparation. The compounding pharmacist should be prepared to thicken the preparation back to its original viscosity. This may easily be accomplished by the addition of up to 5% Versigel® a sodium polyacrylate thickener which forms a gel matrix within the gel or emulsion. If needed, Versigel® should be added before final concentration is reached to avoid changing the concentration of the gabapentin. Note that, although the Pentravan® may be thinned as a result of the addition of the gabapentin, the medication does not loose its liposomal penetration characteristics.

Versigel® (Fagron US) is a thickening, dispersed into a vegetable oil, ready-to-use liquid polymer that may be used over a wide pH range and immediately forms a gel on contact with water. Versigel® can be ordered at Fagron US and is available in volumes of 100 g and 500 g at a transfer price of USD 7.75 (ex works Fagron US; sales price USD 16.48) and USD 26.25 (ex works Fagron US; sales price USD 66.95), respectively. When there is sufficient interest for this product in Europe, distribution may be transferred to Europe. For orders and questions about Versigel® please contact Fagron US.

GABAPENTIN 6% in Pentravan®
Calculated to make 100 g

INGREDIENTS

gabapentin	6.00 g
water	q.s.
Versigel®	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the gabapentin, if necessary with the use of a mortar and pestle.
- Levigate the gabapentin with an appropriate amount of purified water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to reach approximately 90% of final volume, stirring well after each addition of Pentravan®.
- Evaluate viscosity of the preparation and add Versigel® as needed with mixing to obtain desired thickness.
- Add sufficient Pentravan® to bring to final weight.

DISPENSING SYSTEMS
Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS
Store at room temperature.

BEYOND USE DATE
Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS
Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

The Zwitter-ionic nature of gapabentin may overwhelm the Pentravan® emulsion and thin the preparation. In this preparation, Versigel® - a sodium polyacrylate thickener - seeks out the water in the vanishing cream and forms a gel matrix within the cream, thus thickening it. Versigel® may be added drop-wise to thicken the preparation to its original viscosity. Versigel® should be added before final weight is reached so that the concentration of active ingredient is not reduced.

AMITRIPTYLINE

Tricyclic antidepressants are most widely utilized for treatment of depression. Their role in neuropathy has recently emerged. Tricyclic antidepressants such as amitriptyline have been shown to be effective in a variety of pain syndromes such as diabetic neuropathy, sciatic nerve pain, and migraine. Amitriptyline is commercially available only in tablet form, and thus a topical form must be compounded. A case study published in 1999 revealed that transdermal amitriptyline reaches therapeutic systemic levels. The mechanism of action of amitriptyline in pain relief is not known, but it is thought to inhibit the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons.[10] Various formulations and case reports describing the effectiveness of transdermal systems with amitriptyline and have been published.[10,15,18]

Amitriptyline has been shown to be superior to placebo in neuropathic pain management and has a quicker onset of action when employed for analgesia than it has antidepressant activity. An additional benefit of transdermal administration of amitriptyline in neuropathic pain management is that the dose required for analgesia is one half to one third of the antidepressant dose, resulting in lower adverse events profile; but adverse events still exist, including dry mouth, constipation, and cardiac adverse events.[20]

Transdermal absorption relies upon lipid solubility of the medication; the greater the lipid solubility, the greater the transdermal absorption. Amitriptyline is a very suitable candidate for transdermal delivery given its highly lipid-soluble nature. This characteristic results in absorption in a lipid environment, as well as excellent binding to tissues and plasma proteins.[18,22]

In a case report of a patient receiving oral amitriptyline to treat both chronic pain and depression, there was no change in the relief of chronic pain when the route was changed from oral to transdermal. However, while the transdermal route achieved the same response as the oral route, the patient experienced fewer adverse events. The prescribing physician noted no improvement in depression; however, the patient reported an elevation in mood as well as a decrease in pain level. Although efficacy between oral and transdermal administration of amitriptyline seems to be equivalent, the improvement in compliance achieved by transdermal administration is strongly associated with lessened adverse events, making it a good solution the problems attributed to oral administration of amitriptyline.[22]

Tips and tricks

The Zwitter-ionic nature of amitriptyline HCl may overwhelm the Pentravan® emulsion and thin the preparation. The compounding pharmacist should be prepared to thicken the preparation back to its original viscosity. This may easily be accomplished by the addition of up to 5% Versigel®, a sodium polyacrylate thickener which forms a gel matrix within the gel or emulsion. If needed, Versigel® should be added before final concentration is reached to avoid changing the concentration of the amitriptyline HCl. Note that, although the Pentravan® may be thinned as a result of the addition of the amitriptyline HCl, the medication does not loose its liposomal penetration characteristics.

Versigel® (Fagron US) is a thickening, dispersed into a vegetable oil, ready-to-use liquid polymer that may be used over a wide pH range and immediately forms a gel on contact with water. Versigel® can be ordered at Fagron US and is available in volumes of 100 g and 500 g at a transfer price of USD 7.75 (ex works Fagron US; sales price USD 16.48) and USD 26.25 (ex works Fagron US; sales price USD 66.95), respectively. When there is sufficient interest for this product in Europe, distribution may be transferred to Europe. For orders and questions about Versigel® please contact Fagron US at.

AMITRIPTYLINE 2% in Pentravan®
Calculated to make 100 g

INGREDIENTS

amitriptyline HCl	2.00 g
water	q.s.
Versigel®	q.s.
Pentravan®	q.s. ad 100.0 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the amitriptyline HCl, if necessary with the use of a mortar and pestle.
- Levigate the amitriptyline HCl with an appropriate amount of purified water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to reach approximately 90% of final volume, stirring well after each addition of Pentravan®.
- Evaluate viscosity of the preparation and add Versigel® as needed with mixing to obtain desired thickness.
- Add sufficient Pentravan® to bring to final weight.

DISPENSING SYSTEMS
Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS
Store at room temperature.

BEYOND USE DATE
Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS
Use as prescribed. In general, 1 g should be applied to the site of pain, each 4 to 6 hours. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

The Zwitter-ionic nature of amitriptyline HCl may overwhelm the Pentravan® emulsion and thin the preparation. In this preparation, Versigel® - a sodium polyacrylate thickener - seeks out the water in the vanishing cream and forms a gel matrix within the cream, thus thickening it. Versigel® may be added drop-wise to thicken the preparation to its original viscosity. Versigel® should be added before final weight is reached so that the concentration of active ingredient is not reduced.

MORPHINE

Morphine has been widely utilized in pain management and provided in numerous delivery systems. Typically used in end-of-life cases, morphine can be delivered by intravenous, subcutaneous, and oral routes. However, these routes may pose problems for caregivers and patients. Injectable delivery of morphine sulfate can be uncomfortable for the patient and increase risk of complications such as infection and phlebitis. Oral administration may not be feasible as patients may have difficulty swallowing. Application to the skin for transdermal drug absorption is much more convenient for caregivers and assumes less risk for patients. The choice to use transdermal administration of morphine sulfate is usually based on demonstrated improvement of quality-of-life rather than on concerns of efficacy.

Topical morphine administration has been reported to provide rapid relief of cutaneous and other localized pain in a series of six patients receiving palliative care. Relief of diffuse chronic arthritic pain in several case studies has been reported too.[2,3]

The benefit of transdermal administration of morphine has been studied in two different types of pain: cancer-related pain and pain from decubitus ulcers. Due to varied bioavailability through the skin, transdermal administration of morphine does not usually replace traditional, invasive delivery methods for ongoing cancer-related pain.[2,3] However if tolerability and convenience issues arise, many end-of-life pain patients utilize frequent applications of transdermal morphine to manage pain. Topically administered morphine has been efficacious in instances of open wounds such as decubitus ulcers in bedbound patients.[4]

Although the systemic benefits of transdermal morphine have not been well established, use of transdermal morphine may provide relief for some patients, especially in end-of-life care, where quality-of-life is the most important concern for the patient.[2,3]

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MORPHINE SULFATE 5% in Pentravan®
Calculated to make 100 g

INGREDIENTS

morphine sulfate	5.00 g
water	q.s.
Pentravan®	q.s. ad 100.00 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the morphine sulfate, if necessary with the use of a mortar and pestle.
- Levigate the morphine sulfate with an appropriate amount of water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS
Metered pump, EMP jar with attachment, pre-filled syringe, ointment jar.

STORAGE INSTRUCTIONS
Store at room temperature.

BEYOND USE DATE
Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS
Use as prescribed. In general, 1 g should be applied, as needed. Areas for application are the area of pain, or non-hairy, thin-skinned area. The inner wrist or ankle are good sites as the capillary bed is just below the skin in these areas. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

Morphine sulfate preparations should be protected from exposure to light and air.

FENTANYL CITRATE

Fentanyl citrate has been widely utilized in pain management and is available commercially as an injection, a transdermal patch, and as a buccal dosage form (sucker, in the US). Transdermal application certainly provides efficacy and avoids the invasive procedure of injection. In the U.S., duplication of a commercially available dosage form is forbidden, however compounding pharmacist may provide fentanyl citrate in Pentravan® when a patient exhibits contact dermatitis due to the adhesive on the commercially manufactured patch.

Tips and tricks

If compounded transdermal fentanyl citrate is prescribed, use of the Accutenth® syringe dispenser becomes an added benefit. This device delivers 0.1 gram per actuation of the device. This allows the pharmacist to include the smallest usual dose of fentanyl citrate to be contained in 0.1 gram of Pentravan®. Should a greater increment of that dose be needed, multiple actuations may be applied. In a compounded preparation, there is no slow or sustained release of the drug. Instead, multiple doses are delivered throughout the day.

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FENTANYL 12.5 µg/0.1 g in Pentravan®
Calculated to make 10 g

INGREDIENTS

fentanyl *citrate*	1.963 mg
water	q.s.
Pentravan®	q.s. ad 10.00 g

PROCEDURE

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Weigh and/or measure each ingredient accurately.
- Reduce the particle size of the fentanyl citrate, if necessary with the use of a mortar and pestle.
- Levigate the fentanyl citrate with an appropriate amount of water to form a smooth paste.
- Using geometric addition, add sufficient Pentravan® to bring to final weight, stirring well after each addition of Pentravan®.
- Package and label.

DISPENSING SYSTEMS
Accutenth® syringe.

STORAGE INSTRUCTIONS
Store at room temperature.

BEYOND USE DATE
Per USP monograph <795> on non-sterile compounding, a beyond-use date of up to 30 days may be assigned to creams, ointments, gels, and lotions containing water.

PATIENT INSTRUCTIONS
Use as prescribed. In general the cream should be applied as needed. Areas for application are the area of pain, or non-hairy, thin-skinned area. The inner wrist or ankle are good sites as the capillary bed is just below the skin in these areas. Rub the area for at least one minute until the cream has completely vanished into the skin. Wear a glove or finger cot when applying the cream or wash the hands well to prevent possible transfer of medication to eyes, mouth or to an unintended recipient.

Notes

100 µg fentanyl is equivalent to 157 µg fentanyl citrate. Fentanyl citrate preparations should be protected from exposure to light and air.

REFERENCES

1. Erickson B, Brown S. Pain from arthritis and postpolio syndrome. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 183-186.
2. Bryant-Snure SJ, Muller G. Pain from degenerative disc disease. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 187-190.
3. Mestayer III RF. Pain after spinal infusion. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 191-192.
4. McNulty JP. Update on managing neuropathic pain. *International journal of pharmaceutical compounding*. 2009; 13(3): p. 182-190.
5. Various formulations for analgesic transdermal drug delivery systems. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 185-194.
6. Lehman PA, Raney SG. In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan® cream. *International journal of pharmaceutical compounding*. 2012; 16(43): p. 248-252.
7. Sharma N, Agarwal G, Rana AC et al. A review: transdermal drug delivery system: a tool for novel drug delivery system. *International journal of drug development & research*. 2011; 3(3): p. 70-84.
8. Prausnitz MR, Langer R. Transdermal drug deliver. *Nature biotechnology*. 2008; 26(11): p. 1261-1268.
9. Williams KD. Managing pain with transdermal ketoprofen. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 204.
10. Alexander K, Wynn T. Transdermal gel in the treatment of postoperative pain. *International journal of pharmaceutical compounding*. 2007; 11(3): p. 181-184.
11. Allen LV Jr. Transdermals: the skin as part of a drug delivery system. *International Journal of pharmaceutical compounding*. 2011; 15(4): p. 308-315.
12. Margetts L, Sawyer R. Transdermal drug delivery: principles and opioid therapy. *Continuing education in anaesthesia, critical care and pain*. 2007; 7(5):171-176
13. Franckum J, Ramsay D, Das NG et al. Pluronic lecithin organogel for local delivery of anti-inflammatory drugs. *International journal of pharmaceutical compounding*. 2004; 8(2): p.101-105
14. Barkin R. Topical nonsteroidal anti-inflammatory drugs: the importance of drug, delivery, and therapeutic outcome. *American journal of therapeutics*. 2012. Epub ahead of print.
15. Jones M. Clinical nuggets and pearls: chronic neuropathic pain and opioid tolerance. *International journal of pharmaceutical compounding*. 2002; 6(1): p. 4-6.
16. Cabaleiro J. Assessing and treating neuropathic pain. *Home healthcare nurse: the journal for the home care and hospice professional*. 2002; 20(11): p. 718-723.
17. Vadaurri V. Topical treatment of neuropathic pain. *International journal of pharmaceutical compounding*. 2008; 12(3): p. 182-190.
18. Vail J. Compounding for sports medicine. *International journal of pharmaceutical compounding*. 2004; 8(6): p. 443-447.
19. Murdan S. A review of pluronic lecithin organogel as a topical and transdermal drug delivery system. *Hospital pharmacist*. 2005; 12: p. 267-270.
20. Hodges CJ, Jones TH, Willoughby DL. Transdermal gels in the treatment of diabetic neuropathy. *International journal of pharmaceutical compounding*. 2000; 4(2): p. 91-93.
21. Jones M. Chronic neuropathic pain: pharmacological interventions in the new millennium a theory of efficacy. *International journal of pharmaceutical compounding*. 2000; 4(1): p. 6-15.
22. Scott M, Letrent K, Hager K et al. Use of transdermal amitriptyline gel in a patient with chronic pain and depression. *Pharmacotherapy*. 1999; 19(2): p. 236-239.
23. Paice JA, Von Roenn JH, Hudgins JC et al. Morphine bioavailability from a topical gel formulation in volunteers. *Journal of pain and symptom management*. 2008; 35(3): p. 314-320.

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24. Polonini et al. Evaluation of percutaneous absorption performance for human female sexual steroids intro Pentravan cream. International Journal of Pharmaceutical Compounding. 2014; volume 18 no. 4 July/August.
25. Bourdon et al. Evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital. International Journal of Pharmaceutics.515 (2016) 774-787.
26. Kirilov et al. Ex-Vivo percutaneous absorption of enrofloxacin: Comparison of LMOG organogel vs. Pentravan cream. International Journal of Pharmaceutics. 498 (2016) 170-177.
27. Polonini et al. Transdermal oxandrolone: ex vivo percutaneous absorption study. Current drug delivery. 2016, 13, 000-000.
28. Polonini et al. Transdermal formulations containing human sexual steroids: development and validation of methods and in vitro drug release. Quim. Nova. 2014, volume 37, no.4 720-727.

SUGGESTED READING

- **Fagron - Pentravan® global asset kit** (2017). The Pentravan® global asset kit can be downloaded from the Fagron Brand Portal, accessible through #PentravanGlobalAssetKit.
- Argemi A, Concepcion D, Sampaio de Sousa A et al. Characterization of new topical ketoprofen formulations prepared by drug entrapment in solid lipid matrices. *Journal of pharmaceutical sciences.* 2011; 100(11): p. 4783-4789.
- Dowling TC, Arjomand M, Lin ET et al. Relative bioavailability of ketoprofen 20% in a poloxamer-lecithin organogel. *American journal of health-system pharmacists.* 2004; 61(23): p. 2541-2544.
- Fedele D, Giugliano D. Peripheral diabetic neuropathy: current recommendations and future prospects for its prevention and management. *Drugs*. 1997; 54(3): p. 414-421.
- Godwin D, Fuhrman LC. Enhancement of skin penetration of nonsteroidal anti-inflammatory drugs from extemporaneously compounded topical-gel formulations. *International journal of pharmaceutical compounding*. 1999; 3(6): p. 496-499.
- Jones M. Hospice from a compounding pharmacist's perspective. *International journal of pharmaceutical compounding*. 2006; 10(2), p. 89-93.
- Oberlander K. Fibromyalgia. *International journal of pharmaceutical compounding*. 2000; 4(1): p. 21-23.
- Okyar A, Özsoy Y, Güngör S. Novel formulation approaches for dermal and transdermal delivery of non-steroidal anti-inflammatory drugs. Istanbul university faculty of pharmacy department of pharmacology, Beyazit, Istanbul.
- Pain management. *International journal of pharmaceutical compounding*. 2010; 14(3): p. 183-186.
- Peralta A. Principles of pediatric palliative care and pain control. *International journal of pharmaceutical compounding*. 2007; 11(1): p. 10-15.
- Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. *Yale journal of biology and medicine.* 2010; 83: p. 11-25.
- Vidrine E. Compounding for pain management. *International journal of pharmaceutical compounding*. 1998; 2(2): p. 104-105.
- White P. The changing role of non-opioid analgesic techniques in the management of postoperative pain. *Anesthesia and analgesia.* 2005; 101(55): p. S5-S22.
- Zugerman J, Reed T. Topical pain relief: assessment of patient satisfaction with a novel compound containing at least ketoprofen. *International journal of pharmaceutical compounding.* 2007; 11(6): p. 514-519.

APPENDIX 17
Curriculum vitae Dr. Hugo da Silva Maia Jr.