GATTEFOSSÉ

Veterinary Medicines

With Lipid Excipients

People make our name

ABOUT GATTEFOSSÉ

Gattefossé is a leading provider of excipients and formulation solutions to healthcare industries worldwide. Our company history - of over 130 years - is built on a commitment to our customers to deliver the highest quality products and technical support. In parallel to developing innovative formulation applications, Gattefossé has worked diligently to guarantee the pharmaceutical qualification of its excipients.

GATTEFOSSÉ LIPID EXCIPIENTS

The lipids and fatty acids used in the production of Gattefossé excipients are derived strictly from raw materials of vegetable origin.

Excipients are obtained by the esterification of fatty acids with alcohols - glycerol, polyglycerol, propylene glycol and polyethylene glycol - and by the alcoholysis of vegetable oils and fats with glycerol, polyethylene glycol and propylene glycol.

Expertise in oleo-chemistry has enabled the development of a range of functional excipients with different thermal, rheological and textural properties and a wide spectrum of solubility characteristics.

VETERINARY MEDICINES

In veterinary medicine oral, topical and parenteral formulations and dosage forms have specific challenges to overcome:

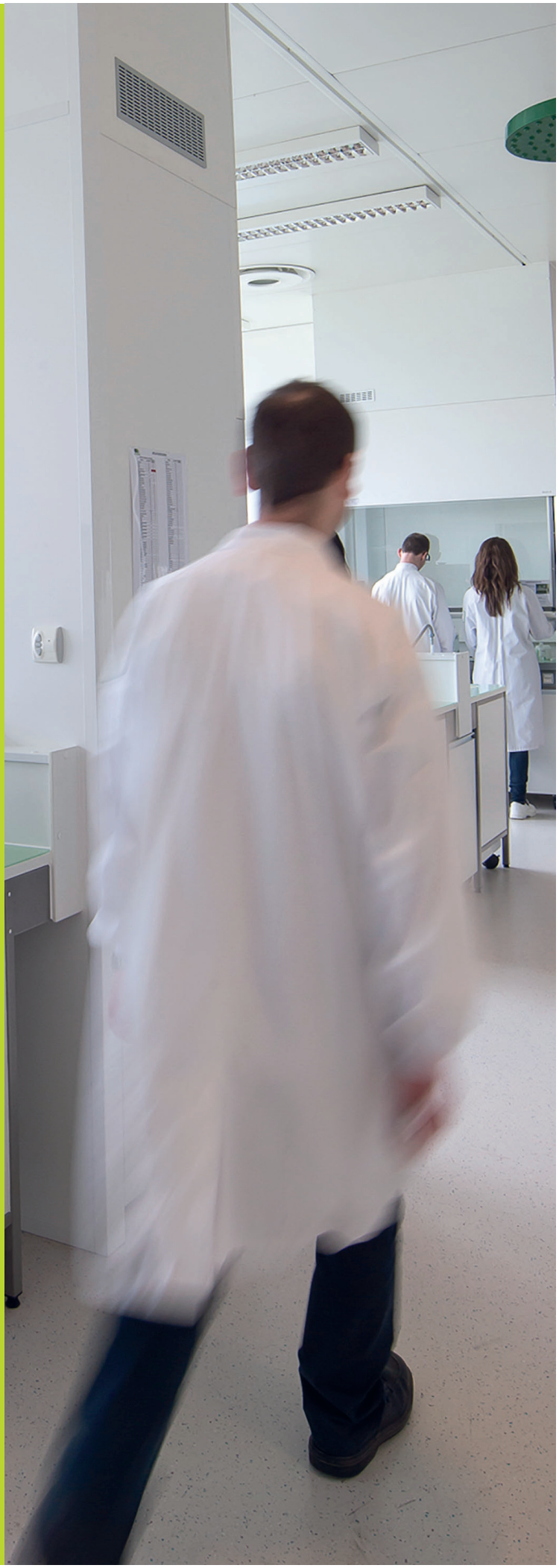
- In domestic animals, **palatability** and **administration** issues are key challenges in developing effective treatments.
- In food producing animals, **residue levels** and delivering therapeutic efficacy with **reduced dosing frequency** are primary concerns.

Functional lipid excipients provide straightforward and innovative approaches for all these challenges.

Our lipid excipients are extremely safe and are used in both human and veterinary medicines, where their functionality delivers measurable advantages in terms of drug delivery and manufacturing.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **Ch.P.:** Chinese Pharmacopoeia; **DEGEE:** Diethylene glycol monoethylether; **DMF:** Drug Master File (Type IV); **DSHEA:** Dietary Supplement Health & Education Act; **EP:** European Pharmacopoeia; **FCC:** Food Chemical Codex; **FDA:** Food and Drug Administration; **FPA:** Food Producing Animals; **GRAS:** Generally Recognized As Safe; **HLB:** Hydrophilic Lipophilic Balance; **IID:** FDA Inactive Ingredient Database; **IM:** intramuscular; **JPE:** Japanese Pharmaceutical Excipients; **JSFA:** Japanese Standard of Food Additives; **MRL:** Maximum Residue Limit (European Regulation); **NFPA:** Non-food Producing Animals; **NSAID:** Non-Steroidal Anti-Inflammatory Drug; **O/W:** Oil in Water; **PEG:** Polyethylene glycol; **SC:** subcutaneous; **USFA:** US Food Additive; **USP-NF:** US Pharmacopoeia-National Formulary; **W/O:** Water in Oil



Contents

Oral drug delivery

Lipid excipients provide solutions to many of the common drug delivery challenges in oral veterinary medicine, including taste-masking, solubility enhancement and management of food effects.

A variety of standard processing techniques can be used depending on lipid excipient properties including direct compression/wet granulation and melt techniques (solid dispersion, prilling, granulation and extrusion).

Dosage form flexibility

- **Tablets, mini-tablets and chewable tablets**
- **Granules**
- **Solutions and pastes**
- **Emulsions/suspensions**

Precedence of use

In tablets, glyceryl dibehenate is used as a lubricant for example in enalapril tablets.

In pastes, a mixture of PEG stearates/ethylene glycol stearate is used with the antibiotic colistin.

In solutions, DEGEE is used to solubilize vitamins in food supplements.

For food-producing animals, anthelmintic treatments are often delivered as a suspension: caprylocaproyl polyoxylglycerides is used as water soluble surfactant or propylene glycol monocaprylate (type II) as a water insoluble surfactant.

Taste-masking

Finely atomized lipid excipients are virtually taste and odor-free. They are inert and compatible with most active and inactive ingredients including flavors, aromas, surfactants and plasticizers.

They are ideal for use in melt processes (coating/granulation) or in a solid dispersion (extrusion/spray cooling etc.).

Lubrication

Compritol® 888 ATO has specific physicochemical properties that deliver manufacturing advantages for oral solid dosage forms.

Products	Functionality	Advantages
Compritol® 888 ATO	Lubricant	Efficacy is independent of mixing time and speed. Does not affect tablet hardness, disintegration time or drug dissolution rate. Decreases ejection forces and improves compressibility. Inert and widely compatible with other ingredients.

Modified release

Sustained release matrix tablets and mini-tablets are straightforward to produce using Compritol® 888 ATO. A lipid matrix tablet is insoluble and non-digestible, it is not affected by changes in pH, it does not dissolve or erode and drug release is controlled by diffusion.

Compritol® 888 ATO is supplied as a ready-to-use powder for use in direct compression or in a granulation process (wet/melt) or by the formation of a solid dispersion (hot melt extrusion, spray cooling).

Product	Functionality	Advantages
Compritol® 888 ATO	Modified release agent	High physiological resistance (pH variation, hydrodynamic stress). Suitable for highly water soluble API. Drug release is easily modulated. Provides additional taste-masking. Non hydroscopic - good storage stability.

Further information is available in our Melt Processes Documentation, Lubricant Brochure and Sustained Release Formulation Guideline.

Solubility and bioavailability enhancement

The application of lipid-based formulations in solubility and bioavailability enhancement is well documented. Lipid excipients improve oral drug delivery by improving drug solubility and dissolution and by normalizing physiological variability including food effects.

Lipid excipients can:

- Increase the solubility of active ingredients and nutraceuticals in gastrointestinal fluids.
- Increase absorption by maintaining compounds in a dissolved state within the gastro-intestinal tract.

Gattefossé excipients can be used in binary mixtures as solubilizing vehicles and in self-(micro) emulsifying formulations, comprising single or multiple excipients.

Products	Functionality	HLB
Gelucire® 48/16*	Water soluble surfactant	12
Labrasol® ALF	Water dispersible surfactant Forms fine (micro)emulsion	12
Gelucire® 44/14*	Water dispersible surfactant Forms fine (micro)emulsion	11
Gelucire® 50/13*	Water dispersible surfactant Forms fine (micro)emulsion	11
Labrafil® M 1944 CS	Water dispersible surfactant Forms coarse emulsion	9
Capryol™ 90	Water insoluble surfactant (co-surfactant)	5
Lauroglycol™ 90	Water insoluble surfactant (co-surfactant)	3
Plurol® Oleique CC 497	Water insoluble surfactant (co-surfactant)	3
Labrafac™ Lipophile WL 1349	Oily vehicle	1
Maisine® CC	Oily vehicle	1
Peceol™	Oily vehicle	1
Transcutol® V	Solvent	-

* Semi-solid products

Further information is available in our Formulation Guidelines for Solubility and Bioavailability Enhancement.

Topical drug delivery

In topical formulation, excipients are used to improve drug delivery by:

- Solubilizing poorly soluble active ingredients, improving **skin penetration** and, in some cases, formation of a **drug depot**.
- Providing emulsifying power and high stability and resolving challenges associated with heat sensitive API, low/high pH and enabling the use of high concentration of oil and alcohols.
- Improving product **texture** and **application properties**.

Dosage form flexibility

+ **Spot-on, pour-on, spray**
+ **Gel, ointment, cream, lotion**
+ **Shampoo**
+ **Patch (transdermal)**

Precedence of use

For companion animals, fipronil-based insecticide is delivered as a spray, pour-on or spot-on using DEGEE as a solubilizer. For cattle, caprylocaproyl polyoxylglycerides are used in pour-on containing moxidectin and triclabendazole as anthelmentic agents.

DEGEE is also used in solutions containing corticosteroids and in sprays containing prednisolone and hexetidine.

In shampoos, caprylocaproyl polyoxylglycerides are used as solubilizers to treat dermatitis.

Selected solubilizers and skin penetration enhancers

Gattefossé solubilizers are reported to improve skin penetration and drug flux.

Transcutol® V is an excellent multifunctional excipient approved by European regulatory authorities for veterinary medicines and biocidal products for use in food producing animals.

It is widely used in topical medicines for both farmed and domestic animals due to its excellent solubilizing properties and safety.

Safety advantage

Several skin irritation and sensitization tests prove that Transcutol® is non-irritant and non-sensitizing. Other studies show Transcutol® to provide superior dermal tolerability compared with other solvents commonly used in topical formulation (Papakostantinou et al, 2007).

Transcutol® mechanism of action

- **Skin penetration:** The high solubilization power of Transcutol® enables high drug loading and the generation of a steep concentration gradient down which the drug is "pushed" into the skin.
- **Drug flux:** Increasing drug concentration in the formulation by increasing its solubility can promote drug flux. Transcutol® may also enhance drug flux across the *stratum corneum* by diffusing into it and altering its solubility parameter (Harrison et al, 1996).
- **Drug retention:** Transcutol® formulated with certain drugs enables the formation of an intra-cutaneous drug depot by inducing swelling in the lipid bilayer of the *stratum corneum* (Ritschell et al, 1991).

Further information is available in our Lipid Excipients for Topical Drug Delivery Brochure.

Products	Functionality	HLB	Dosage form	Advantages
Transcutol® V	Solvent	-	Spot-on Pour-on/spray Gel, ointment, (micro)emulsion	Excellent universal solubilizer. Skin penetration modulator. Synergistic vehicle effects with sebum. Drug dependent depot effect. Extensive toxicology and safety dossier.
Labrasol®	O/W surfactant	12	Gel, ointment, (micro)emulsion	Unique composition delivers excellent solubilizing power and skin penetration enhancement. Extensive toxicology and safety dossier.
Labrafil® M 1944 CS	O/W surfactant	9	Ointment, (micro)emulsion	Excellent in association with Tefose® 63.
Capryol® 90	W/O surfactant	5	Gel, ointment, (micro)emulsion	Excellent solubilizer/skin penetration enhancer for many actives (e.g. anti-fungal agents and NSAIDs).
Lauroglycol™ 90	W/O surfactant	3	Ointment, (micro)emulsion	Extensive toxicology and safety dossier.
Labrafac™ Lipophile WL 1349	Oily vehicle	1	Ointment, (micro)emulsion	Highly versatile vehicle with no MRL restrictions.
Labrafac™ PG	Oily vehicle	1	Ointment, (micro)emulsion	Highly versatile vehicle with no MRL restrictions.

Selected emulsifiers

Products	Functionality	HLB	Dosage form	Advantages
Tefose® 1500	O/W emulsifier	10	Fluid lotion/ spray	Polyvalent, compatible with all types of oils.
Tefose® 63	O/W emulsifier	9.5	Cream	Excellent mucosal tolerance. Easy to formulate.
Plurol® Diisostearique*	W/O emulsifier	4.5	(Micro) emulsion fluid	PEG-free emulsifier ideal for use with heat sensitive actives (cold formulation process).

*Liquid form.

Injectable drug delivery

Functional excipients provide distinct advantages in injectable drug delivery.

- In subcutaneous and intramuscular injections, oily vehicles and lipid-based micro-emulsions are reported to improve injection site tolerance (reduced pain and swelling).
- Solubilizing properties prevent injection site precipitation associated with high dose "one-shot" therapies.
- Suspensions and (micro)-emulsions can be formulated to provide controlled/sustained drug release.
- Lipid soluble compounds can be delivered in oil-in-water emulsions which are rapidly absorbed at the injection site and provide a depot of active dissolved in small oil droplets.

Precedence of use

In injectable solutions, DEGEE is widely used as a solubilizer. Precedence of use exists with antibiotics such as oxytetracycline or florfenicol, and also with anti-inflammatory agents such as ketoprofen or tolfenamic acid.

In injectable suspensions, precedence of use exists for medium-chain triglycerides as an oily vehicle for antibiotics such as amoxycillin. Ceftiofur hydrochloride is formulated with oleoyl polyoxylglycerides as water dispersible surfactant.

Selected excipients for injectable formulations

Products	Functionality	HLB	Administration route	Advantages
Transcutol® V	Solvent	-	IM, SC	Excellent solubilizing vehicle. Proven low irritancy. Extensive toxicity studies and safety dossier.
Labrafac™ Lipophile WL 1349	Oily vehicle	1	IM, SC	Associated with intramuscular depot. Good association with Labrafil® M 1944 CS.
Labrafac™ PG	Oily vehicle	1	IM, SC	Suspension vehicle with broad API compatibility. Well characterized excipient with long history of use.
Labrafil® M 1944 CS	Water dispersible surfactant	9	IM, SC Intra-mammary	Good injection site tolerance. Low irritancy.

Gattefossé excipients are not guaranteed apyrogen or sterile. Lipid excipients in formulations can be sterilized by common procedures including autoclave, filtration and ionizing radiation.

Due to their oleochemical nature, Gattefossé excipients are classified as excipients with low potential for microbial contamination and certification can be provided.

Depending on Pharmacopœia requirements for veterinary injectable dosage forms, customers should apply the most appropriate sterilization method for the active ingredient/finished product form.

Excipient regulatory status

Gattefossé International Regulatory Affairs Department is on hand to help with any questions you may have regarding the use of our excipients in veterinary medicines.

Products	Full chemical description	Additional regulatory information	Market reference
Capryol™ 90	Propylene glycol monocaprylate (type II) NF	DMF/FCC/USFA/ JSFA	Oral FPA (v) Topical (h)
Compritol® 888 ATO/ Pellets	Glycerol dibehenate EP Glyceryl dibehenate NF Glyceryl behenate Ch.P.	DMF/IID/GRAS/ FCC/JSFA	Oral (h) Topical (h) Ocular (h)
Geleol™ Mono and Diglycerides NF	Glycerol monostearate 40-55 (type I) EP Mono and diglycerides NF	DMF/IID/E471/ FCC/GRAS/JSFA No MRL restrictions (EU)	Topical (v) Oral (h) Topical (h)
Geloil™ SC	Mixture of refined soya bean oil (and) glyceryl distearate (and) polyglyceryl-3 dioleate	All components are food grade materials. No MRL restrictions (EU)	Nutraceutical (h)
Gelucire® 44/14	Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF	DMF/IID/USFA	Oral (h) Nutraceutical (h)
Gelucire® 48/16	Macrogol stearate EP (pending) Polyoxyl stearate (type I) NF Polyethylene glycol monostearate JPE	DMF No MRL restrictions (EU)	Oral (h) Topical (h)
Gelucire® 50/13	Stearoyl macrogol-32 glycerides EP Stearoyl polyoxyl-32 glycerides NF	DMF/IID/USFA	Oral FPA (v) Oral (h)
Labrafac™ Lipophile WL 1349	Triglycerides medium-chain EP Medium chain triglycerides NF Medium chain fatty acid triglyceride JPE	DMF/IID/DSHEA/ JSFA No MRL restrictions (EU)	Injectable (v) Oral (h) Topical (h)
Labrafac™ PG	Propylene glycol dicaprylocaprate EP Propylene glycol dicaprylate/dicaprate NF	IID/DSHEA/ USFA/JSFA/E477 No MRL restrictions (EU)	Oral (h)
Labrafil® M 1944 CS	Oleoyl macrogol-6 glycerides EP Oleoyl polyoxyl-6 glycerides NF	DMF/IID	Injectable (v) Oral (h) Topical (h)
Labrasol® ALF	Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF	DMF/IID	Topical (v) Topical (h) Oral (h)
Lauroglycol™ 90	Propylene glycol monolaurate (type II) EP/NF	DMF/IID/DSHEA/ FCC/USFA/E477/ JSFA No MRL restrictions (EU)	Oral (h) Topical (h) Nutraceutical (h)
Maisine® CC	Glycerol monolinoleate EP Glyceryl monolinoleate NF	DMF/IID/FCC/ E471/JSFA No MRL restrictions (EU)	Oral (h)

Products	Full chemical description	Additional regulatory information	Market reference
Peceol™	Glycerol monooleate (type 40) EP Glyceryl monooleate (type 40) NF	DMF/IID/GRAS/ FCC/E471/JSFA No MRL restrictions (EU)	Oral (h) Topical (h) Nutraceutical (h)
Plurol® Diisostearique	Triglycerol diisostearate EP Polyglyceryl-3-diisostearate NF	DMF/IID	Topical (h)
Plurol® Oleique CC 497	Polyglyceryl-3 dioleate NF	DMF/IID/E475/ FCC/JSFA/USFA No MRL restrictions (EU)	Oral (h) Topical (h)
Precirol® ATO 5	Glycerol distearate (type I) EP Glyceryl distearate NF	DMF/IID/FCC/ GRAS/JSFA	Oral (h)
Tefose® 63	Mixture of PEG-6 stearate NF/JPE/ EP pending (and) ethylene glycol palmitostearate EP/NF/JPE (and) PEG-32 stearate NF/JPE/EP pending	DMF/IID	Oral FPA (v) Topical (h)
Tefose® 1500	Mixture of PEG-6 stearate NF/JPE/EP pending (and) PEG-32 stearate NF/JPE/EP pending	DMF/IID/ No MRL restrictions (EU)	Topical (h)
Transcutol® V	Highly purified diethylene glycol monoethyl ether EP/NF	DMF/IID No MRL (EU) (all ruminants, porcine)	Oral FPA (v) Topical (v) Injectable (v)

(v) approved veterinary medicine

(h) approved human medicine

Gattefossé is not an approved manufacturer or supplier of feed additives, premixtures and compound feed-stuff. Therefore we do not support the use of our excipients in animal feed.

For more information please see Gattefossé Regulatory Summary Table: veterinary medicines, biocidal products/pesticide products available at www.gattefosse.com

Technical support

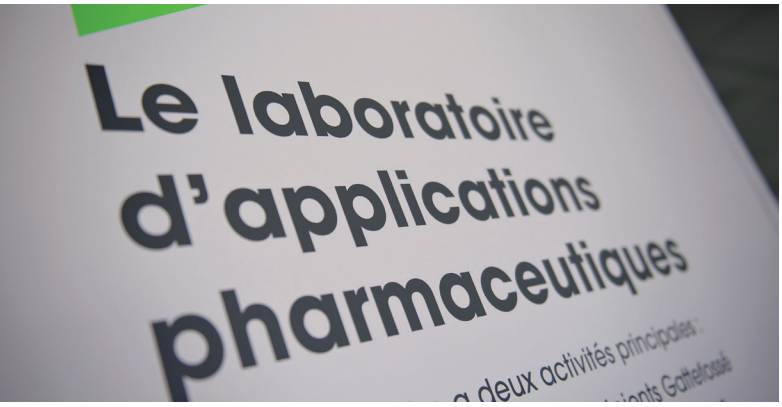
Our applications laboratories in France, India, China and US are at your service to provide technical support and formulation feasibility assessment.

We have many years of experience of formulating with our products with both experimental and model drugs. We are committed to answering your questions on formulation, regulatory, safety, scale-up issues and precedence of use as quickly and as comprehensively as we can.

We can reduce your development time by providing straightforward formulation guidelines for oral, dermal, rectal and vaginal dosage forms as well as access to extensive databases comprising hundreds of validated placebo or model API formulations.

If you need practical laboratory assistance, the services we are able to offer include solubility screening, basic formulation development, texture optimisation and sensorial analysis.

Please contact your local Gattefossé representative
or email us at: infopharma@gattefosse.com



Bibliography

Ahmed, I., & Kasraian, K. (2002). Pharmaceutical challenges in veterinary product development. Advanced drug delivery reviews, 54(6), 871-882.

Cunningham F. et al. (Eds) (2010) Comparative and Veterinary Pharmacology. Handbook of Experimental Pharmacology. Review (199): Springer Verlag Berlin Heidelberg.

Harrison J.E. et al. (1996) The Relative Effect of Azone® and Transcutol® P on Permeant Diffusivity and Solubility in Human *Stratum Corneum*. Pharmaceutical Research Vol 13, No 4, 542-546.

Magnusson B.M. et al. (2001) Veterinary drug delivery: Potential for skin penetration enhancement. Advanced Drug Delivery Reviews. (50): 205 - 227.

Medlicott N. J. et al. (2004) Sustained release veterinary parenteral products. Advanced Drug Delivery Reviews. (56): 1345 - 1356.

Papakostantinou E. et al. (2007) Efficacy of 2 weeks' application of theophylline ointment in psoriasis vulgaris. Journal of Dermatological Treatment 16 (3): 169-170.

Ritschel W. A. et al. (1991) Development of an Intracutaneous Depot for Drugs Binding, Drug Accumulation and Retention Studies, and Mechanism of Depot. Skin Pharmacol. 4 : 235-245.

GATTEFOSSÉ

VETERINARY MEDICINES-GB-GC-9LM2-CT-(2071VM)

www.gattefosse.com

Corporate Headquarters
36 chemin de Genas - CS 70070 - 69804 Saint-Priest Cedex - **France**
+(33) 4 72 22 98 00

People make our name