LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Vectatone, 1 %, cream
(penciclovir)

SE/H/1410/01/MR

This module reflects the scientific discussion for the approval of Vectatone. The procedure was finalised at 2014-06-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Novartis Sverige AB has applied for a marketing authorisation for Vectatone, 1 %, cream. The active substance is penciclovir. Penciclovir is a substituted guanine analogue (9-(4-hydroxy-3-hydroxymethylbutyl)guanine), similar to aciclovir (the first anti-HSV agent), with antiviral activity against herpes simplex virus (HSV) types 1 and 2 and against varicella zoster virus.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Vectatone is presented in the form of a cream containing 10 mg penciclovir. The excipients are
Paraffin, soft white
Paraffin, liquid
Cetostearyl alcohol
Propylene glycol
Macrogol cetostearyl ether 1000
Iron oxide, red and yellow (E172) and
Water, purified

The cream is filled in 2 g and 5 g aluminium tube closed with a plastic screw cap (polyethene). The tube is lined on the inside with an epoxy-phenol resin lacquer.

II.2 Drug Substance

There is no monograph for Penciclovir neither in Ph. Eur.

The structure of penciclovir has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Vectatone cream is formulated using excipients described in the current Ph Eur, except for red and yellow iron oxide which are controlled according to USP-NF.

The product development has taken into consideration the physico-chemical characteristics of the active substance. The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The pharmacological activity of penciclovir (PCV) against human herpes virus has been tested in *in vitro* studies including HSV-1, HSV-2, varicella zoster virus and Epstein-Barr virus. The data provided in this dossier is based on literature and published by Boyd et al 1993. The comparison of penciclovir with acyclovir (ACV) is also included in the evaluation of the pharmacological activity. The IC_{50} values for PCV against HSV-1 in primary cultures of human keratinocytes and a continuous keratinocyte cell line were 0.19 and 0.13 µg/mL, respectively. The corresponding values for ACV against HSV-1 were 0.10 and 0.62 µg/mL, respectively.

Penciclovir has been studied in animal models, where animals were infected with herpes simplex virus using topical and oral administration demonstrating that PCV was active by topical route against HSV infection.

It can be concluded that the pharmacology of penciclovir has been studied in appropriate *in vitro* and *in vivo* models. Since penciclovir was approved for treatment of HSV already late 1990s, there is extensive clinical experience of using penciclovir against HSV and the pharmacological activity of penciclovir against HSV has been confirmed in human.

Safety pharmacology of penciclovir has been studied appropriately in *in vitro* studies and in animal studies, which did not indicate any safety concern. Additionally based on extensive clinical use, the safety of penciclovir is adequately studied and does not raise any risk for humans.

III.2 Pharmacokinetics

Percutaneous absorption of penciclovir 1% cream was studied in the rat. The results from the absorption study in the rat with penciclovir 1% cream showed that percutaneous absorption was low. Therefore, a very low systemic exposure to penciclovir was anticipated during therapeutic use of penciclovir 1% cream. This prediction has been confirmed in clinical studies.

III.3 Toxicology

Toxicology of penciclovir was evaluated late 1990s when Vectavir 1% cream was authorised in many countries worldwide. Later on a duplicate called Vectatone 1% cream and tinted cream have been authorised. In the nonclinical toxicology program for penciclovir studies of general toxicity, genotoxicity, and reproductive toxicology, local tolerance, antigenicity have been included.

General toxicology studies revealed kidney and testes as target organs for toxicology when the compound was given via oral or intravenous administration route to rats and monkeys. These

findings were associated with high systemic exposure to penciclovir. Due to low absorption of penciclovir through the skin these findings are not considered relevant to patients when the treatment is topical. The duration of treatment is also short.

The results from in vitro and in vivo genotoxicoly studies indicated mutagenicity or increased micronuclei in *in vivo* test. However, the risk for genotoxicity to humans can be considered low, since penciclovir has not been detected in plasma of human subjects following topical application of the cream. Therefore it can be concluded that the risk of Vectatone 1% cream for genotoxicity to humans is low. Mutagenicity or genotoxicity studies have not been performed with the tinted cream, but the two pigments, yellow iron oxide and red iron oxide are inert and also used in food and cosmetic products and do not carry risk for genotoxicity. It can be concluded that genotoxic potential for Vectatone 1% coloured cream is similar to Vectatone 1% cream.

Reproductive toxicology studies following intravenous administration were performed in the rat and rabbit. Effects on fertility and reproductive performance were studied in the rat indicating no effects that could be related to the treatment with penciclovir. No treatment-related effects were observed in untreated F_1 generation rats either. There were no adverse effects on the course and outcome of pregnancy. Results from the pre- and postnatal studies in the rat did not indicate any treatment-related effects in the offspring.

Local tolerance of penciclovir was studied in two animal species in 4-week dermal repeat-dose studies. The results showed that penciclovir 1% cream was considered mildly irritant. The Vectatone 1% coloured cream was studied in an acute dermal irritation study in rabbits and was considered to be non-irritant after dermal application. It can be concluded from the results of these studies that Vectatone 1% coloured cream is not expected to be irritant in humans.

Antigenicity of the penciclovir coloured cream has been studied in a maximisation test in the guinea pig. The results showed that the coloured cream dose not exhibit skin sensitization potential. It can be concluded that the coloured cream has been appropriately studied for skin sensitization potential.

Impurities have been qualified in toxicology studies. More detailed impurity profile and their qualification is presented in the Quality section.

III.4 Ecotoxicity/environmental risk assessment

The log K_{OW} is taken as a surrogate for the bioaccumulation potential. The octanol/water partition coefficient of the penciclovir is -1.62 (at about 25^{o}C, Method OECD 107). Penciclovir showed low bioaccumulation potential as indicated by the Log Kow of less than 4.5.

Penciclovir, exhibiting an IC_{50} of 1230 mg/L, was not toxic to activated sludge microorganisms. It is not readily biodegradable but is inherently biodegradable and is not expected to persist in the environment.

Predicted Environmental Concentration (PEC)

The PEC of penciclovir, shown in the table below, is calculated according to the formula using default values given in EMEA/CHMP/SWP/4447/00.

PEC surfacewater= $\frac{\text{DOSE ai* Fpen}}{\text{WASTEwinhab*DILUTION}}$

Active ingredient	Maximum daily dose of AI (mg)	PEC calculation using default values Fpen= 0.01 WASTEWinhab =200 DILUTION=10	PEC surfacewater (µg/L)
Penciclovir	5	$\frac{5*0.01}{200*10}$	0.025

Because the PEC of the active ingredient, without considering removal from sewage water treatment plant is >0.01 µg/L, phase II evaluation on the environmental risk of penciclovir has been carried out. However, most of the penciclovir used are expected to reach waste water treatment plants where penciclovir is efficiently removed, removal rate >87%. Taking into account removal at waste water treatment plants, PEC would be 0.003 µg/l.

Aquatic effect studies

Ecotoxicity studies and calculated PNEC

TEST	OECD	EU	Toxicity
Algae growth inhibition	201	C.3.	Not available
Algae toxicity (Estimation model using ECOSAR, EPi Suite v3, EPA)			224mg/L
Fish , acute toxicity Bluegill sunfish (lepomis macrochirus) (96h)	203	C.1.	LC_{50}:>986mg/L NOEC: >986mg/L
Daphnia toxicity Daphnia magna (48h):	202	C.2.	NOEC: 496mg/L EC_{50}: 820mg/L

* PNEC is calculated with an assessment factor 1000 on the most sensitive species data among the available data.

Calculation of PNECs using assessment factors

The PNEC is calculated with an assessment factor 1000 on the most sensitive species data among the available data. A PNEC of 0.2 mg/L was obtained using the data from the algae toxicity data obtained by in silico structure activity analysis.

Outcome of Tier A fate and effects analysis

Surface water assessment

The PEC in surface water is estimated from the maximum daily dosage of the product without taking into consideration removal from sewage water treatment plant. The $PNEC_{surfacewater}$ was derived from the NOEC from the algae toxicity SAR model with an assessment factor of 1000.

$PEC_{surfacewater}$ = 0.025µg /L
$PNEC_{surfacewater}$ = 200 µg /L
The risk ratio PEC surface water /PNEC = 0.0001

The risk ratio using PEC surface water assuming no removal showed a value of 0.0001, far less than 1. The risk ratio was obtained with the acute studies and as assessment of 1000. It is not likely that chronic toxicity data would compromise the risk ratio to reach >1. Furthermore, the PEC based on maximum daily dosage is an overestimate of the concentration released to the environment. Most of the penciclovir used are expected to reach waste water treatment plants where penciclovir is efficiently removed (from >87%). Penciclovir resulting from the use of Penciclovir 1% cream is therefore not likely to represent a risk to the aquatic environment.

Groundwater assessment

The PEC in groundwater was estimated to be 0.25 that of the $PEC_{surfacewater}$.

The PEC groundwater is 0.00625ug/l. Because the PEC ground water is <0.01ug/L, further evaluation is not required. Penciclovir resulting from the use Penciclovir 1% cream is therefore not likely to represent a risk to the aquatic environment.

Conclusion drawn by the Applicant - Tier A risk assessment

Penciclovir, with a IC_{50} of 1230mg/L for toxicity to microorganisms in sludge and PEC from product of 0.025µg /L is not expected to reduce action of microorganisms in sewage treatment plants. Penciclovir is efficiently removed (>87%) in waste water treatment plants. Taking into account removal at waste water treatment plants, PEC is 0.003 µg/L.

The risk ratio using PEC surface water assuming no removal showed a value of 0.0001, less than 1.

The n-octanol/water partition (log Kow) of penciclovir is less than 4. Bioaccumulation is therefore not expected.

Penciclovir is efficiently removed (>87%) in waste water treatment plants Taking into account removal at waste water treatment plants, PEC is 0.003 µg/L.

The environmental risk assessment for Vectatone 1% cream concludes that penciclovir is not likely to represent a risk to the environment. This applies also the Vectatone 1% coloured cream.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Vectatone is a cream for the topical treatment of labial herpes infections and the pharmacokinetic assessment is, thus, mainly of interest from a safety perspective, to assess systemic exposure. There is no product with penciclovir available for systemic use, however, the substance famciclovir is an oral pro-drug to penciclovir and is indicated for use in varicella Zoster infections and genital herpes infections. In these indications, a much higher penciclovir exposure is achieved compared with topical use in labial herpes infections.

The systemic absorption of penciclovir was assessed in a study in healthy subjects, when applied repeatedly to damaged skin under conditions of overdose and occlusion. No detectable concentrations of penciclovir could be observed in any plasma or urine samples from the twelve subjects included in the study, even when penciclovir was applied under “worst-case” conditions. With an improved analytical method, a lower LLOQ could possibly have been achieved. However, there are no indications of safety problems after topical use based on extensive clinical experience with penciclovir cream. Furthermore, based on comparisons with i.v. penciclovir or oral famciclovir the exposure after topical use is very low. Clinical dosing with the recommended 250 mg t.i.d dose of oral famciclovir would result in approximately 1000 times greater systemic exposure.

The clinical data for penciclovir cream are mainly based on the experience gained with the original penciclovir 1% formulation, while the current application for Vectatone concerns a tinted cream, the only difference being addition of biologically inert pigments to the cream. No human pharmacokinetic or clinical data are available for the Penciclovir 1% tinted cream but the experience from the use of the original un-tinted penciclovir 1% cream is extensive. It is agreed that the addition of two biologically inert pigments to the cream are not expected to affect the efficacy and safety profile. In non-clinical studies, there was no difference in penetration through lip skin between the original and tinted cream formulations.

Data on basic pharmacokinetic properties of penciclovir are based mainly on studies with i.v. administration. Penciclovir is bound to human plasma proteins at relatively low extent (<20%). *In vitro* studies with both intact and tape-stripped human skin have confirmed penetration of penciclovir into different skin layers, with higher concentrations in the epidermis than the dermis. Penciclovir has a non-complicated elimination, being mainly renally excreted as unchanged drug.

Consistent with the renal elimination, somewhat increased exposure is observed in subjects with impaired renal function and elderly, which is considered without clinical relevance considering the overall low exposure to penciclovir following topical administration. The lack of pharmacokinetic data in hepatic impairment is acceptable, considering the low systemic absorption and the renal elimination. Concerning the paediatric population, the SmPC informs that safety and efficacy of Vectatone in children below 12 years of age has not been established.

There is limited data on pharmacokinetic interactions, which is also deemed acceptable considering the low extent of systemic absorption.

IV.2 Pharmacodynamics

Penciclovir is phosphorylated in the infected cells (host neurons, epidermal cells and dermal cells) by viral and host thymidine kinases and converted to the active drug penciclovir triphosphate. The phosphorylated drug inhibits viral deoxyribonucleic acid (DNA) polymerase and thus viral replication. In uninfected cells, penciclovir is not readily phosphorylated and does not inhibit cellular DNA synthesis at antiviral concentrations.

Penciclovir is a well-known antiviral agent with an extensive clinical experience.

IV.3 Clinical efficacy

The clinical trials demonstrating efficacy and safety consisted of two randomised, double-blind, placebo-controlled trials (Study No. 39123/024 and Study No. 39123/025 hereafter named studies 024 and 025) of penciclovir 1% cream for the treatment of subjects with RHL. The two placebo-controlled trials were originally used to support the key efficacy claims for the original penciclovir 1% cream.

There were no major differences in the patient population in studies 024 and 025 with regard to baseline demographics and disease characteristics between subjects treated with penciclovir 1% cream and placebo. Penciclovir- and placebo-treated patients applied an average of 8.4 doses per day during the first four days. The placebo cream consisted of the formulation used as vehicle only.

The main evidence of efficacy was the proportion of patients who had lost classical lesions of RHL by Day 6, 7, and 8. Classical lesions are lesions that demonstrate the typical herpetic features of vesiculation, ulceration, or crusting; all patients who reported any of these stages after initiation of therapy contributed to this analysis. Statistically significant efficacy was demonstrated in both performed clinical trials assessed by both investigator and patient (see table below). However, RHL is a self-healing condition and topical antiviral therapy has a limited efficacy, while the effect of placebo is considerable. In spite of this, antiviral products are widely used in RHL and the clinical experience is extensive.

Subgroup analysis was performed to investigate the effect of treatment efficacy with regard to the lesion stage at which the treatment was initiated. In both studies 024 and 025, the application of the study drug during erythema or prodrome stages was considered as *early* initiation of treatment; application of the study drug at a papule stage or later was considered as *late* initiation of treatment. The efficacy of penciclovir 1% cream was statistically significantly better than placebo regardless of the stage of the lesion at which therapy was initiated. As could be expected, the efficacy of penciclovir 1% cream was higher in subjects who were compliant with study medication.

After the first approval of penciclovir 1% cream, 4 efficacy studies have been published. Overall, the results in the supportive studies (data not shown) confirm the results obtained in studies 024 and 025. The design of the studies is somewhat different from the pivotal studies which make a direct comparison of the results difficult.

Table. Comparison of efficacy in the placebo-controlled trials

Study & efficacy parameter		Penciclovir		Placebo				
Resolution of classical lesions		**%**		**%**		**OR**	**95%CI**	**P**
Study 024	Patient, Day 6	66.7		56.2		1.65	1.31-2.08	<0.001
	Patient, Day 7	78.0		68.3		1.75	1.34-2.23	<0.001
	Patient, Day 8	85.1		78.5		1.67	1.25-2.24	0.001
	Investigator, Day 6	70.2		58.5		1.76	1.39-2.22	<0.001
	Investigator, Day 7	80.7		70.1		1.88	1.44-2.44	<0.001
	Investigator, Day 8	86.7		80.4		1.67	1.23-2.26	0.001
Study 025	Patient, Day 6	68.8		57.6		1.57	1.23-1.99	<0.001
	Patient, Day 7	78.3		68.9		1.57	1.20-2.04	0.001
	Patient, Day 8	84.2		75.9		1.58	1.18-2.11	0.002
	Investigator, Day 6	69.8		59.2		1.52	1.19-1.94	0.001
	Investigator, Day 7	79.2		71.3		1.45	1.10-1.91	<0.008
	Investigator, v 8	85.3		78.4		1.48	1.09-2.00	0.012
Duration of lesions [days]		**Median**	**Q1-Q3**	**Median**	**Q1-Q3**			**P**
Study 024	Patient	3.3	1.6-5.6	4.0	1.9-6.3			0.0008
	Investigator	4	2-6	4	2-7			0.0002
Study 025	Patient	3.0	1.2-5.2	3.6	1.6-6.3			0.0011
	Investigator	3	2-5	4	2-6			0.0106
Time [days] to: Resolution of classical lesions		**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**HR**	**95%CI**	**P**
Study 024	Patient	4.8	3.2-6.5	5.5	3.7-7.4	1.33	1.18-1.49	0.0001
	Investigator	5	4-7	6	4-8	1.25	1.12-1.40	0.0001
Study 025	Patient	4.4	3.0-6.5	5.3	3.5-7.8	1.29	1.14-1.45	0.0001
	Investigator	5	4-7	6	4-8	1.19	1.06-1.35	0.0040
• Loss of lesion pain								
Study 024	Patient	3.8	2.4-5.9	4.4	2.9-6.5	1.24	1.10-1.39	0.0004
	Investigator	3.9	2.4-5.9	4.4	2.9-6.5	1.21	1.08-1.37	0.0014
Study 025	Patient	3.1	1.9-5.1	4.0	2.3-6.6	1.32	1.17-1.50	0.0001
	Investigator	3.2	1.9-5.2	4.0	2.3-6.7	1.30	1.15-1.48	0.0001
• Cessation of viral shedding								
Study 024		3	2-3	3	2-4	1.35	1.10-1.64	0.0033
Study 025		3	2-3	3	2-4	1.47	1.20-180	0.0002

CI=Confidence interval; HR=Hazard ratio; N=Number of patients; P=Statistical significance at 5% level;
Source: [Module 2.7.3 (2012) Summary of Clinical Efficacy]

Data source: [Study 024 = cited as Study 1B, Study 025 = cited as Study 2B]

IV.4 Clinical safety

The key safety population in the two pivotal trials (studies 024, 025) consisted of 1516 patients who were instructed to apply penciclovir 1% cream every 2 h whilst awake (7 to 9 times/day) for 4 days.

A summary of AEs per body system, occurring at a frequency of >1% during the time period from the first dose of study medication to within 30 days after the last dose in the two placebo controlled studies with penciclovir 1% cream, demonstrated that the overall AE incidence was similar for the penciclovir group compared to the placebo group (see table below). The AEs were in general mild in severity. Headache was the most commonly reported AE, followed by

application site reaction/hypoaesthesia. For both of these AEs, incidences were comparable in the penciclovir and the placebo group.

Table. Most frequently affected body systems □ □safety population in pivotal Studies 024 and 025 (reported for >1% patients)

	Penciclovir		Placebo	
Patients studied	**N**	**%**	**N**	**%**
Total no. of patients studied	1516	100.0	1541	100.0
Total no. of patients with AE	302	19.9	351	22.8
Body system				
Central and Peripheral Nervous System	131	8.6	148	9.6
Gastrointestinal System	44	2.9	42	2.7
Respiratory System	45	3.0	48	3.1
Resistance Mechanisms[#]	45	3.0	43	2.8
Body as a Whole General	37	2.4	54	3.5
Application Site	20	1.3	28	1.8
White Cell / Reticuloendothelial	20	1.3	20	1.3
Musculoskeletal System	16	1.1	16	1.0
Reproductive Female	15	1.0	15	1.0
Skin and Appendages	13	0.9	20	1.3

N=Number of patients;

Safety population: includes patients who applied at least one dose of the study drug.

All adverse experiences were coded from the verbatim term according to the WHO Adverse Reaction Terminology (ART) dictionary by body system and preferred term [Study 1B, 2B].

N=number of patients # AEs included in the body system "Resistance Mechanism" are abscess, herpes simplex infection, bacterial infection, fungal infection, viral infection, monoliasis, genital monoliasis, otitis media, and upper respiratory tract infection.

No patient was withdrawn from the studies due to an AE that was assessed as related to penciclovir. There was no evidence of photo-irritancy or sensitivity.

Four patients reported SAEs (3 treated with penciclovir recipients, 1 treated with placebo). None of the AEs are considered related to treatment with penciclovir (personality disorder, gastrointestinal disorder, otosclerosis). One patient treated with placebo (vehicle control) had an allergic reaction. Two deaths were reported, both suicides, which are not considered related to treatment with penciclovir.

Concerning safety in special populations, there are no data with the penciclovir cream formulation in children or adolescents, however oral data with famciclovir in adolescents indicate no difference in adverse events compared to adults. The systemic exposure from topical application is negligible. Safety from preclinical studies with i.v. penciclovir indicates no cause for concern. Therefore, inadvertent use of penciclovir cream during pregnancy is unlikely to be a safety concern. There are data in elderly from studies 024 and 025. The data indicates no difference in recommended usage or adverse events in elderly than in younger patients. However, the amount of safety data in elderly is rather sparse.

The exposure of patients post marketing to the original penciclovir 1% cream is extensive, estimated as 29.4 million patients (period 01 Jan 2007 to 30 Jun 2013). The cumulative exposure to the tinted penciclovir 1% cream is about 1.7 million patients (from launch April

2011 to 30 Jun 2013). Altogether, the clinical experience with penciclovir 1% cream formulations is considered large.

Spontaneous adverse event reports from 04 Jun 1996 to 30 Jun 2013 reported to the MAH's safety database included a total of 880 cases, describing 1706 adverse events (AEs). 'General disorders and administration site conditions' was the most common AE (45 % of all AEs reported for all cream formulations and 67 % for the tinted cream only) (see tables below). Within this SOC, the most frequently reported clinical events were various application site reactions (e.g. Application site reaction, Application site pain, Application site swelling), all of which are listed in the current Reference Safety Information (RSI).

Table. Summary of adverse events by System Organ Class All cream formulations

System Organ Class (SOC)	Total number of AEs	Most common AEs (≥10)
General disorders and administration site conditions	769	Drug ineffective (176)
		Therapeutic response decreased (138)
		Condition aggravated (83)
		Application site reaction (71)
		No adverse event (54)
		Application site pain (42)
		Application site erythema (25)
		Application site swelling (24)
		Pain (24)
Skin and subcutaneous tissue disorders	210	Blister (36)
		Erythema (35)
		Pruritus (27)
		Rash (12)
		Rash erythematous (12)
Gastrointestinal disorders	205	Lip swelling (50)
		Oral discomfort (21)
		Lip pain (17)
		Hypoaesthesia oral (15)
		Cheilitis (14)
Infections and infestations	171	Oral herpes (76)
		Herpes simplex (71)
Injury, poisoning and procedural complications	139	Accidental exposure to product (30)
		Exposure during pregnancy (29)
		Wrong technique in drug usage process (17)
		Scar (12)
Nervous system disorders	99	Burning sensation (29)
		Headache (19)
		Paraesthesia (19)
		Hypoaesthesia (14)
Psychiatric disorders	31	Intentional drug misuse (20)
Immune system disorders	24	Hypersensitivity (24)
Eye disorders	17	NA
Surgical and medical procedures	15	Off label use (15)
Respiratory, thoracic and mediastinal disorders	10	NA
Vascular disorders	5	NA
Musculoskeletal and connective tissue disorders	3	NA
Pregnancy, puerperium and perinatal conditions	3	NA

System Organ Class (SOC)	Total number of AEs	Most common AEs (≥10)
Blood and lymphatic system disorders	1	NA
Cardiac disorders	1	NA
Hepatobiliary disorders	1	NA
Investigations	1	NA
Social circumstances	1	NA
Total	1706	NA

Time period for the data: 04 Jun 1996 (first launch) until 30 Jun 2013 (data-lock point).
AE=adverse event; NA.= not applicable

Table. Summary of adverse events by System Organ Class (tinted cream only)

System Organ Class (SOC)	Total number of AEs	Most common AEs (≥2)
General disorders and administration site conditions	37	Drug ineffective (9) Application site pain (6) Condition aggravated (5) Application site erythema (3) Application site swelling (2)
Skin and subcutaneous tissue disorders	5	Pruritus (2)
Gastrointestinal disorders	4	NA
Infections and infestations	4	Oral herpes (4)
Nervous system disorders	4	Burning sensation (3)
Immune system disorders	1	NA
Injury, poisoning and procedural complications	1	NA
Total	56	NA

Time period for the data: April 2011 (first launch) until 30 Jun 2013 (data-lock point).
NA= not applicable

Although the number of AEs is slightly higher for the tinted cream formulation, the addition of a biologically inert iron dye to the tinted cream is not expected to alter the safety profile. Overall, considering the large number of patients exposed to penciclovir 1% cream formulations, the number of AEs reported is low. Thus, penciclovir 1% cream formulations have a favourable safety profile.

No new non-serious adverse events were identified in the post marketing data, as application site reactions, hypersensitivity, and dermatitis allergic are already included in the RSI. Herpes simplex and Oral herpes (MedDRA term for recurrent herpes labialis) are the approved indication for use of penciclovir, and are considered pre-existing conditions.

Other safety topics investigated were overdose, abuse potential, rebound or withdrawal and use in pregnancy and lactation. No new safety concerns were identified regarding either topic.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Vectavir, national procedure, type II variation Dnr 2122:2011/71115. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Vectatone, 1%, cream is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Vectatone, 1%, cream was successfully finalised on 2014-06-12.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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