

Clínicals Analysis

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• Germany

Labor für Auftragsanalytik und Forschung

HWI ANALYTIK GmbH, Hauptstraße 28, 76764 Rheinzabern

Bull Pharma Vertrieb
Kurt Teubner
Basler Straße 115

79115 Freiburg



Hauptstraße 28
76764 Rheinzabern
Tel: 07272-9309-0
Fax: 07272-9309-26
email: hwi@analyt@aol.com

Rheinzabern, 26.11.1997

Analysenzertifikat

Präparat: Skin-Cap Spray
Ch.-B.: K-39
Auftraggeber: Herr Teubner

Laborcode: 2505
Eingang: 24.11.1997
Bestimmung: 25.11.1997

Gehalt Clobetasol-17-propionat:

Gefunden: nicht nachweisbar nicht nachweisbar = no detectable

Bestimmungsgrenze: 0,5 mg / kg

Methode:

HPLC-Bestimmung mit UV-Detektion nach der Methode des externen Standards.



Dr. Stefan Wissel

HWI ANALYTIK GmbH - Geschäftsführer: Dr. Stefan Wissel, Dr. Hanns Haberlein, Lothar Wissel
Sitz der Gesellschaft: 76764 Rheinzabern, Hauptstraße 28 - Registergericht: Amtsgericht Landau HRB 1388 Kandel
Bank: Sparkasse Gernsheim-Kandel (BLZ 251440) Kto.-Nr.23001233

• Spain



Centro de
Investigaciones
Biológicas

C/ Velázquez, 144. 28006. Madrid (España)
Tels. 34 1 - 561 18 00. Fax 34 1 - 562 75 10

We have performed analysis of clobetasol propionate in several samples of SKIN-CAP (Spray) (batch L-11, L-13, L-14 and L-16), determining molecular weight with a Bruker Biflex MALDI-TOF Mass Spectrometer (Bruker Analytical Systems Inc.) with a N_2 laser (337 nm wavelength) and a pulse of 3 ns. Accelerations for the analyzed samples were 19.5 and 20.0 KV for linear and reflector TOF-MS, respectively.

Results showed the presence of a peak at 468 (M+H) and 325 in the sample which contained added clobetasol propionate as internal standard. On the other hand, only the 325 peak was detectable in the sample without the added standard.

Therefore, we could not detect the presence of clobetasol propionate in any of the samples (without added standard) analyzed by this method.

Madrid, 15 August, 1997

Dr. Antonio Martín González
Senior Investigator of CSIC

Tilman Sánchez Elsner



ANALYSIS REPORT FOR - BIOCEUTICALS PTY. LTD.

History:

Date 9/9/97 Sample L-26 arrived in laboratory. (delivered by Dr B.Massoud)
22/9/97 Reference Std of Clobetasol Propionate arrived as above.
23/9/97 Sample Reference Std analysed by Mass Spec
Spike sample and extraction begun.
24/9/97 Sample extraction and analysis of L-26 (ID 65997)
Analyses and report generated.

Samples for MS analysis: Skin Cap Spray L-26 Sample ID: 65997
Clobetasol Propionate Std Sample ID: 107997

Method:

The sample was run on a Finnigan/MAT TSQ 4600
The Mass Spectrometer was operated in the Chemical ionisation (CI) mode
monitoring for positive ions. Peak detection was in centroid mode scanning Q1
from m/z 100 to m/z 550 in a .45 sec scan time.
The peaks created in the ion chromatograms from the mass spectrometer have
been smoothed and all mass spectra generated are background subtracted.

Sample Preparation:

1. The contents of two cans of SKIN-CAP spray were discharged into a 250ml glass vessel.
2. An Aliquot of 20ml was spiked with Clobetasol Propionate at 0.05%.
3. A further 20ml aliquot was taken as the unspiked sample.
4. The samples were then filtered to remove most of the Zinc Pyrithione.
5. Each sample was separately put onto the rotary evaporator to remove any ethanol, approx 15min.
6. To each sample a solution of methanol:water (95:5) in the proportion of mysterate:water 1:3 was added.
7. The samples were mixed thoroughly for 5min, then sonicated for 20min.
8. The sample were then put into clean centrifuge tubes and spun at 2500g for 20min.
9. The Methanol layers of both extracts were transferred into clean flasks and then put onto rotary evaporator for 15min each.
10. The remaining material was transferred to a centrifuge tube and spun at 250g for 20min.
11. The aqueous layer was removed and put onto the rotary evaporator to remove all the water.
12. To the material remaining 10ml of ethanol was added and mixed gently.
13. The ethanol was then transferred into a clean vial for analysis by MS

Results:

See attached MS Chromatograms and Spectra

File BM0124997 is Clobetasol Propionate reference std (#107997).

The trace on the ion chromatogram (page 5) shows a peak at scan #105, the Mass Spectrum of this is plotted on (page 6) and shows a protonated molecular ion at m/z 467. Page 7 is a different plot format of the same mass spectrum as (page 6).

The file BM0224997 (page 8) is a Blank run of ethanol and a limited mass chromatogram of 467 shows no significant level the ion trace produces an ion count of 17 ions (this is electronic noise). The mass spectrum (page 9) at scan 124 at amplification factor 20 shows only noise peaks.

The file BM0324997 is the Sample extract of (#065997) the ion trace (page 10) in this case producing 5240 ion counts at scan #150, the Mass Spectrum of this is plotted on (page 11), and the peak at #164 is plotted (page 12), it can be seen that neither spectrum matches with the Clobetasol Propionate spectrum plotted (page 6).

Conclusion:

From the mass spectral investigation of the Skin-Cap L26 ID 065997 sample supplied is negative for Clobetasol Propionate in this sample.

Analysis Conducted by Bruce Tattam.

Bruce Tattam
Facility Manager
Mass Spectrometry Analytical Facility
Department of Pharmacy A15
University of Sydney 2006



West Yorkshire Analytical Services

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Dr Duncan Campbell B.Sc, D. Phil, M. Chem.A., C. Chem.,
M.R.S.C., Registered Analytical Chemist
Public Analyst and Agricultural Analyst

Our reference: DC/NW

16 March, 1998

Skin Cap Ltd
The Moorings
Waterside Industrial Park
Stourton
Leeds
LS10 1DG

REPORT

Sample: Skin Cap 50 g Cream
Lot No: L-13
Mfg. Date: 9/97
Expiry Date: 9/00
Lab Ref.: K08704
Submitted by: Mr Ken Holbrook
On: 9th March 1998

Analysis to test for the presence of Clobetasol Propionate.

Procedure: 1 gram of the material was dissolved in 25 millilitres of a 75:25 mixture of methanol and water. The solution was filtered prior to HPLC analysis under the following conditions:

Column: 15cm Sperisorb SODS2
Eluant: Methanol/water (75:25)
Flow Rate: 1ml/minute
Detector: Thermo Quest UV 3000 rapid scanning detector
(200-350 nm)
Injection volume: 10 microlitres
Column temperature: 20°C

Results

Under the conditions above a Clobetasol Propionate standard eluted at 5.63 minutes. No peak of this retention time was produced from an injection of the sample solution.

Conclusion

No indication has been found of the presence of Clobetasol Propionate in the sample.

Duncan Campbell

Dr D J Campbell
Public Analyst





West Yorkshire Analytical Services

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Dr. Duncan Campbell B.Sc, D. Phil, M. Chem.A, C. Chem,
M.R.S.C., Registered Analytical Chemist
Public Analyst and Agricultural Analyst

Our reference: DC/NW

16 March, 1998

Skin Cap Ltd
The Moorings
Waterside Industrial Park
Stourton
Leeds
LS10 1DG

REPORT

Sample: Skin Cap 150 ml Shampoo
Lot No: L-28
Expiry Date: Sep 02
Lab Ref.: K08053
Submitted by: Mr Ken Holbrook
On: 9th March 1998

Analysis to test for the presence of Clobetasol Propionate.

Procedure: 1 gram of the material was dissolved in 25 millilitres of a 75:25 mixture of methanol and water. The solution was filtered prior to HPLC analysis under the following conditions:

Column: 15cm Spherisorb 5ODS2
Eluant: Methanol/water (75:25)
Flow Rate: 1ml/minute
Detector: Thermo Quest UV 3000 rapid scanning detector (200-350 nm)
Injection volume: 10 microlitres
Column temperature: 20°C

Results

Under the conditions above a Clobetasol Propionate standard eluted at 5.63 minutes. No peak of this retention time was produced from an injection of the sample solution.

Conclusion

No indication has been found of the presence of Clobetasol Propionate in the sample.

Dr D J Campbell
Public Analyst





West Yorkshire Analytical Services

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Dr Duncan Campbell B.Sc, D.Phil, M. Chem.A., C. Chem.,
M.R.S.C., Registered Analytical Chemist
Public Analyst and Agricultural Analyst

Our reference: DC/DS

19 February, 1998

Skin Cap Ltd
The Moorings
Waterside Industrial Park
Stourton
Leeds
LS10 1DG

REPORT

Sample: Skin Cap 100ml spray
Lot No.: L-28
Expiry Date: Sep 02
Lab Ref.: K07952
Submitted by: Mr Ken Holbrook
On: 17th February 1998

Analysis to test for the presence of Clobetasol Propionate.

Procedure: 1 gram of the material was dissolved in 25 millilitres of a 75:25 mixture of methanol and water. The solution was filtered prior to HPLC analysis under the following conditions:

Column: 15cm Spherisorb 5ODS1
Eluant: Methanol/water (75:25)
Flow Rate: 1ml/minute
Detector: Thermo Quest UV 3000 rapid scanning detector
Injection volume: 10 microlitres
Column temperature: 20°C

Results

Under the conditions above a Clobetasol standard eluted at 2.94 minutes. No peak of this retention time was produced from an injection of the sample solution.

Conclusion

No indication has been found of the presence of Clobetasol Propionate in the sample.

Duncan Campbell

Dr D J Campbell
Public Analyst

\\ARRPORTS\IT001-KUK07952.DOC

Page 1 of 1



ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΥΠΟΥΡΓΕΙΟ ΟΙΚΟΝΟΜΙΚΩΝ
ΓΕΝΙΚΟ ΧΗΜΕΙΟ ΚΡΑΤΟΥΣ
Γ' ΧΗΜΙΚΗ ΥΠΗΡΕΣΙΑ ΑΘΗΝΩΝ

Αθήνα, 20-11-1997..

Αρ. Πρωτ.: 4982

Ταχ.Δ/ση: Αν. Τσόχα 16, 115 21
Τηλέφωνο: 6428211/Εσωτ.232,233
FAX: 6465123
TELEX: 0218311

ΠΡΟΣ: Ανωτάτη Επιτροπή
Τελων. Αμφισβητήσεων

ΘΕΜΑ : Σκεύασμα SKIN-CAP
ΣΧΕΤ. : Εγγραφο 150/19-11-1997 ΑΕΤΑ.

Απαντώντας στο ανωτέρω σχετικό, με το οποίο μας υποβάλατε με το σκεύασμα SKIN-CAP καθώς και τις εργαστηριακές εξετάσεις των εργαστηρίων : α) Κρατικού Πανεπιστημίου του Michigan (Η.Π.Α.), β) Πανεπιστημίου του Σίδνεϋ (Αυστραλίας), γ) Ολλανδών Φαρμακοποιών (Ολλανδίας) και δ) Ε.Ο.Φ. (Ελλάδας), με το ερώτημα κατά πόσον το σκεύασμα περιέχει την κορτικοστεροειδή ουσία Clobetasol propionate, σας κάνουμε γνωστά τα κάτωθι :

Εκ της μελέτης των παραστατικών συνάγεται ότι :

- Σε ένα πολύπλοκο σκεύασμα, όπως το ανωτέρω, δεν είναι εύκολο να αποφανθεί κανείς για την ύπαρξη ή μη της Clobetasol propionate με μόνο χρωματογραφικές μεθόδους, διότι, και άλλες ουσίες είναι δυνατόν να έχουν τους αυτούς χρόνους κατακράτησης με την εν λόγω ουσία κάτω από συγκεκριμένες χρωματογραφικές παραμέτρους. Η ανίχνευση καθίσταται δυνατή εάν κανείς εργασθεί επισταμένως παραλλάσσοντας τις χρωματογραφικές παραμέτρους, όπως π.χ. τα υγρά ανάπτυξης και έκλουσης και με διαφορετικές στήλες και υποστρώματα. Αυτήν την τεχνική πραγματοποίησε το Ολλανδικό εργαστήριο.
- Βασικά η επιβεβαίωση της παρουσίας ή μη της Clobetasol propionate στα σκεύασμα αυτού του είδους αποτελεί αντικείμενο έρευνας με εξειδικευμένες τεχνικές και εξειδικευμένες συσκευές Φασματογράφου Μάζας, που δεν διαθέτουν τα εργαστήρια του Γ.Χ.Κ.
- Και τα τρία πιο πάνω αναφερόμενα εργαστήρια του εξωτερικού, το ένα με εξειδικευμένες τεχνικές χρωματογραφίας (Ολλανδικό) και τα άλλα δύο με τεχνικές Μάζας (Αμερικής και Αυστραλίας) καταδεικνύουν αναλυτικά ότι η εν λόγω ουσία Clobetasol propionate δεν περιέχεται στο σκεύασμα SKIN-CAP της εταιρείας CANTASSIUM HELLAS S.A.

Ο Προϊστάμενος της Δ/σης
Παναγιώτης Μαυρίκος

• Greece (translation)

GREEK DEMOCRACY
MINISTRY OF FINANCE
GENERAL STATE OF CHEMISTRY
THIRD CHEMICAL DEPARTMENT OF ATHENS

Athens 20th of November, 1997

Protocol No. : 4992

Post - Address: Anastasios Tsoha 16
Postal Code: 115 21
Telephone: 01 642821
Internal: 232 - 233
Facsimile: 01 6465123
Telex: 02 18311

To: The Highest Committee
of Custom Disputes

SUBJECT : The Product SKIN - CAP
RE : Document No. 150/19/11/1997 HCCD (AETA)

In response to the above mentioned documents with which you deposited along with the product SKIN - CAP, as well as the laboratory examinations from the following laboratories:

- A. The State Laboratory of Michigan (USA),
- B. The Laboratory of the University of Sidney (Australia),
- C. The Chemical Laboratory of Holland (Holland) and
- D. The Hellenic Pharmaceutical Administration (EOF, Greece).

In relation to the question of whether or not the above product contains traces of Corticosteroid Clobetasol Propionate, we acknowledge the following:

According to the studies which were completed by the above Laboratories,
the examinations showed that:

- In a complicated product such as the above, it is not easy to have proper results, due to the fact that this product is complex and nobody can make a clear decision on whether or not there are traces of Clobetasol Propionate within by using only Chromatographic Methods. This is so, due to the fact that there are other substances, in addition to the Clobetasol Propionate, with the same properties and the same time retention as the above substance.
- It is possible to examine the product in depth for traces of this substance. If someone were to undergo such an examination, they must do so carefully under very controlled circumstances, by changing the chromatographic parameters, like, for example, to increase the liquid and the pull which must be in varying columns and layers. This is technical data which was used by Holland's Laboratories.
- Basically, the certification of whether or not there is any Clobetasol Propionate present in this type of product is subject to further study with specialized techniques and apparatus for the Phasmatometrical mass, equipment in which the laboratories of the General State Chemistry do not have.
- In all three of the above mentioned foreign laboratories, the first has specialized technical data of Chromatography (in Holland) and the remaining two have technical data for mass (in the USA and Australia), demonstrating analytically that in reference to the above substance, Clobetasol Propionate, is not present in the product SKIN - CAP which is from the Company Cantassium Hellas SA.

Division Director

Signature (and Stamp)
Panagiotis Mavrikos

- NOTICE : The product SKIN - CAP is produced by the Company CHEMINOVA INTERNACIONAL SA. The Company CANTASSIUM HELLAS SA is only the importer and distributor of this product.



Vyšetření vzorku SKIN-CAS spray na přítomnost clobetasol 17-propionátu

žadavatel:

KOMVET spol. s r.o.
Sadová 576
675 21 Okříšky

specifikace dodaného vzorku:

SKIN-CAP spray 100 ml, šarže M-10, exp. sep-03 (do laboratoře dodáno 9.března 1999)

ANALYTICKÝ POSTUP

a) preanalytická úprava

Vzorek byl skladován při laboratorní teplotě. Před úpravou byl důkladně protřepán. Poté byl za pomoci aplikátoru (součást praxe) nastříkán objem asi 10 ml do kádinky, odplyněn na ultrazvuku a přefiltrován přes mikrofiltr (filter units 25 mm - teflon, 5 mm PTFE - fa Shandon).

b) HPLC metodika

přístroj: kapalinový chromatograf HP 1100 s DAD detektorem (Hewlett-Packard)
kolona: LiChroSpher C18 (250×4, 5 µm, Merck) s předkolonkou (4×4, 5 µm)
mobilní fáze: methanol:voda (0-15 min 65 % MeOH, 15-35 min 65-100 % MeOH)
průtok mobilní fáze: 1 ml/min
detekce: 242 nm
teplota kolony: 20 °C
teplota nártřiku: 20 °C
objem nártřiku: 20 µl

c) analytický standard

clobetasol propionát CAS: 25122-46-7 (čistota 99 %, Sigma)
koncentrace zásobního roztoku - 1 mg/ml v methanolu
desítkovým ředěním byla připravena pětibodová škála standardních roztoků
(v koncentračním rozpětí 0.0001 - 1 mg/ml)

DOKUMENTACE VYĚTŘENÍ

Pro účely vyšetření vzorku byla vyvinuta a validována analytická metoda. Realizovány byly následující kroky dokumentované v příloze:

1. Bylo změřeno absorpční spektrum standardu viz. obr. 1. Pro vlastní měření byla určena vlnová délka 242 nm odpovídající absorpčnímu maximu.
2. Byla optimalizována HPLC separace, viz. obr.2.
3. Byl stanoven lineární rozsah odezvy detektoru (0.0001 - 1 mg/ml), viz. kalibrační graf - obr. 3.
4. Hodnota detekčního limitu odpovídá 0.1 µg/ml, viz. obr.4.
5. Vyšetření reálného vzorku SKIN-CAP spray (100 ml, šarže M-10, exp. sep-03) ilustruje obr. 5.

VÝSLEDEK

V přípravku SKIN-CAS spray nebyla za výše uvedených podmínek vyšetření prokázána přítomnost clobetasol 17-propionátu.

Analýzy provedl : Ing. J.Guziur
Konzultace: Dr. Ing. V. Schulzová

Prof. Ing. J. Hajšlová, CSc.
vedoucí laboratoře

• Czech Republic (translation)

Protocol and Analysis of a SKIN-CAP Spray Sample
to Test for the Presence of Clobetasol Propionate

Applicant:
KOMVET spol.s r.o.
Sadová 576
675 21 Ok_í_ky

Sample:
SKIN-CAP Spray 100 ml, batch M-10, expiry SEP-03
The sample was handed over to the laboratory on March 9, 1999.

ANALYTICAL TECHNIQUE

a) preanalytical condition (preparation of the sample before analysis)
The sample was stored at room temperature in the laboratory. Before handling, it was shaken well. Afterwards, through the applicator which is an integral part of the spray, some 10 ml were let out into a small container. Then there followed the degasification of the sample in ultrasound and the filtration through microfilter (filter units 25 mm - teflon, 5 mm PTFE - fa Shandon).

b) analytical method HPLC
Equipment used: liquid chromatograph HP 1100 with detector DAD (Hewlett-Packard)
Column: LiChroSpher C 18 (250x4,5 mm, Merck) with precolumn (4x4,5 mm)
Eluant: methanol/water (0 - 15 min. 65 % MeOH, 15 - 35 min. 65 - 100 % MeOH)
Flow rate: 1 ml/min.
Detection: 242 nm
Column temperature: 20 °C
Flow temperature: 20 °C
Injection volume: 20 µl

c) analytical standard
Clobetasol propionate CAS: 25122-46-7 (purity 99 %, Sigma)
Concentration of reserve liquid: 1 mg/ml in methanol
Using decimal dilution, there was prepared a five-point scale of standard solutions (with concentrations between 0.0001 - 1 mg/ml).

GRAPHIC EVIDENCE OF THE TESTS

In order to analyse the sample, an analytical method was developed and validated.
The following steps were taken (see graphic evidence enclosed):

1. The standard absorption spectrum has been measured (graph 1). For the proper measurement, there has been determined the corresponding wavelength 242 nm with the maximum absorption.
2. HPLC separation has been optimized (graph 2).
3. There has been determined the extension of the repercussion of the detector (0.0001 - 1 mg/ml) (graph 3 - calibration).
4. The value of the detection limit is 0.1 mg/ml (graph 4).
5. examination of the real SKIN-CAP Spray sample (100 ml, batch M-10, expiry SEP-03) (graph 5).

RESULTS

No indication has been found of the presence of CLOBETASOL PROPIONATE in the preparation SKIN-CAP Spray analysed under the above-mentioned conditions.

Analysis made by: Ing. J. Guziur
Consultant: Dr. Ing. V. Schulzova

Prof. Ing. J. Haj_lova, CSc
Head of the Laboratory

Prague, 20.03.1999

• United Arab Emirates

UNITED ARAB EMIRATES
MINISTRY OF HEALTH



وزارة الشؤون الصحية
وزارة الصحة

إدارة الصيدلة والرقابة الدوائية

الرقم: إص/رد/د/ ٦ - ٣ / ١٦٧٦
التاريخ: ١٩٩٨/٨/٢٩

السادة / المزروعى للتجهيزات الطبية والكيميائية المحترمين
دبى فاكس :- ٠٤/٦٩٠٦١٢
تحية طيبة وبعد.....

م/مستحضر سكن كاب SKIN CAP
من شركة Cheminova

إشارة الى الخطاب الوارد من الادارة العامة لشرطة ابوظبى - قسم الادلة الجنائية - تحت رقم ٢٢٩٥ / سم / ٩٨ والمتضمن عدم وجود مادة Clobestol فى مستحضر سكن كاب (كريم، بخاخ وشامبو)، عليه نفيدكم بأنه لامانع لدينا من بيع المستحضر المذكور اعلاه.

وتفضلوا بقبول تحياتنا.....



د. مريم
مديرة ادارة الصيدلة والرقابة الدوائية

- نسخة لقسم التسجيل الدوائى.
- نسخة لمختبر الرقابة الدوائية.
- نسخة للملف العام.

• **United Arab Emirates (translation)**

United Arab Emirates
Ministry of Health
Direction of Pharmacy and Medicines Vigilance

SKIN-CAP PRODUCTS (CHEMINOVA INTERNACIONAL)

According to the Police General Direction of Abu Dhabi laboratory under number 2295/ SM / 98 which certify the ABSENCE of CLOBETASOL DIPROPIONATE and CLOBETASOL BUTYRATE from the SKIN-CAP PRODUCTS (SPRAY, SHAMPOO and CREAM).

General Director of Pharmacy and Medicines Vigilance

Dr. Mariam

• Saudi Arabia

وزارة الصحة

الجمهورية العربية السعودية
وزارة الصحة

الرقم :
التاريخ :
الشفوعات :

المحترم

المكرم مدير مؤسسة زمو التجارية
السلام عليكم ورحمة الله وبركاته

اشارة الي خطاب مدير المختبر المركزي للدوية والاذوية رقم ٢٧/١/٤٢٨ في
١٤١٩/١/٢٧ هـ والمتضمن عدم وجود مادة Clobetasol في مستحضر Skin Cap Spray من
انتاج شركة Cheminova الاسبانية :
عليه نفيدكم بانه لا مانع من التصرف بالمستحضر المذكور اعلاه .

مع اطيب تحياتي ،،،

مدير عام الرخص الطبية والصيدلة

د/ صباح محمد الرئيس

د/ طلال مناب
اسعد ابراهيم
٩٦٢١٧

17 JUN 1998
ZIMMO TRADING EST.
JEDDAH

• Saudi Arabia (translation)

Kingdom of Saudi Arabia
Ministry of Health

According to the letter of the Director of the Central Laboratory of Medicine and Foods with number 428/1/27 dated 27/1/1419 Hijry which certifying that NO PRESENCE OF CLOBETASOL in the product SKIN-CAP SPRAY produced by Cheminova Internacional.

General Director of Medicine and Pharmacy Licence.

Dr. Sabah Mohammad al rayes

• Holland



Laboratorium der Nederlandse Apothekers

Postbus 30460 - 2500 GR 's-Gravenhage • Tel (070) 362 41 11

A N A L Y S E R A P P O R T

SKIN-CAP, diverse producten

- 1) Crème (50 g) : charge L-12, LNA-registratienummer Z1230
- 2) Shampoo (150 ml) : charge L-24, LNA-registratienummer Z1229
- 3) Spray (100 ml) : charge L-25, LNA-registratienummer Z1228

Doel analyse:

Onderzoek op aanwezigheid van corticosteroiden.

Conform declaratie (bedrukt op de verpakking van de monsters) mogen deze niet aantoonbaar zijn.

Conclusie onderzoek:

Uit chromatografisch onderzoek (DLC en HPLC-DAD) zijn geen aanwijzingen verkregen die wijzen op de aanwezigheid van corticosteroiden.

Datum: 11 september 1997

NAMENS HET LABORATORIUM DER
NEDERLANDSE APOTHEKERS,

O.S.N.M. Smeets, apotheker

• Holland (translation)



Laboratorium der Nederlandse Apothekers Postbus 30460 - 2500 CL 's Gravenhage Tel. (070) 3624111

C E R T I F I C A T E O F A N A L Y S I S

SKIN-CAP, several products:
ESHUIS BODYCARE - HILVARENBEEK - HOLLAND

- 1) Cream (50 g) : batchnumber L-12, LNA-registrationnumber Z1230
- 2) Shampoo (150 ml) : batchnumber L-24, LNA-registrationnumber Z1229
- 3) Spray (100 ml) : batchnumber L-25, LNA-registrationnumber Z1228

Aim of analysis:

Research for the presence of corticosteroids.

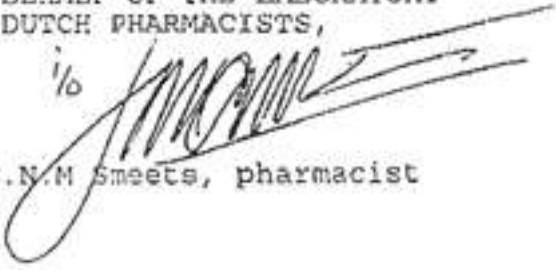
Conform the declared content (as stated on the container of the samples) corticosteroids should not be present.

Conclusion:

From the results of chromatographic analysis (TLC and HPLC-DAD), no indications have become for the presence of corticosteroids in the products mentioned above.

Date: 11 September 1997

ON BEHALF OF THE LABORATORY
OF DUTCH PHARMACISTS,

i/o

O.S.N.M. Smeets, pharmacist



iolab



97/8142-1

Pag. 1 di 1

VERIFICA ASSENZA DEL TRIAMCINOLONE E SUOI DERIVATI (ACETONIDE E DIACETATO)

CONTRATTO N. : 97/146

COMMITTENTE : NOVA RESIUM
C.SO INDEPENDENZA 6
20129 MILANO

CAMPIONE IN ESAME : 'SKIN CAP SIKAY'
29 LOT: L-15

N. DI RICEVIMENTO : RO2108.97 DEL: 06.06.97

N. IDENTIFICATIVO : 97/9645

METODO : HPLC CON RIVELATORE A FOSFORO

DATA INIZIO ANALISI : 30.06.97

DATA FINE ANALISI : 2.07.97

RISULTATI ANALITICI

DETERMINAZIONE	UNITA' DI MISURA	RISULTATO
TRIAMCINOLONE	mg/100ml	non rivelato (1)
TRIAMCINOLONE DIACETATO	mg/100ml	non rivelato (1)
TRIAMCINOLONE ACETONIDE	mg/100ml	non rivelato (1)

(1) Sensibilità del metodo 0.02mg/100ml.

CENTRO DI RICERCA
S.p.A. - Via S. Felice 1
20129 MILANO - Tel. 02/574011
FAX 02/574012

DR. G. COSTANTINI
Via S. Felice 1
20129 MILANO - Tel. 02/574011
FAX 02/574012

DATA EMISSIONE: 3.07.97

DIRETTORE DELLO STUDIO:

Dr. G. Costantini

I risultati contenuti in riferimento esclusivamente al campione provato.
Il presente rapporto può essere riprodotto soltanto per intero.

• Italy (traslation)

BIOLAB

Verify the presence of TRIAMCINOLONE and their derivates (ACETONOIDE and DIACETATE).

Product: SKIN-CAP SPRAY batch L-15

ANALITICAL RESULTS

TRIAMCINOLONE	NON REVEALED
TRIAMCINOLONE DIACETATE	NON REVEALED
TRIAMCINOLONE ACETONOIDE	NON REVEALED

Date 03 - 07 - 97

Dr. G. Costantint

• Malaysia



PUSAT INOVASI DAN PERUNDINGAN UNIVERSITI SAINS MALAYSIA

Innovation and Consultancy Centre
11800 USM Penang, Malaysia

Tel.: 04-6577888 Ext. 3684, 2132

Direct Line: 04-6572407

Fax: 04-6572210

Bil. Kami (*Our Ref.*)

Bil. Tuan (*Your Ref.*)

Tarikh (*Date*)

24th June 1999

SIJIL ANALISIS / CERTIFICATE OF ANALYSIS

Tajuk (*Title*)

Chemical Analysis of "Skin-Cap Spray"

Pelanggan (*Client*)

IMEKS Farmaseutis Sdn. Bhd.
No 2 Jalan 6/33B Batu 6½
Jalan Kepong MWE Commercial Park
52000 Kuala Lumpur

Pencerapan/Komen (*Observation/Comment*)

Spray
Lot : N-4
Exp. : March 2004

Kaedah yang digunakan (*Method used*)

Thin Layer Chromatography

Keputusan (*Results*) (Gunakan muka surat baru sekiranya perlu / *Use separate sheet if necessary*)

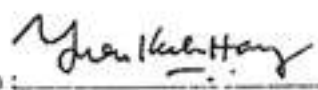
The following steroids were not detectable ; (detection limit : 1mcg)

- | | |
|------------------------------|---------------------------|
| 1. Betamethasone | 6. Hydrocortisone |
| 2. Betamethasone-17-valerate | 7. Hydrocortisone acetate |
| 3. Dexamethasone | 8. Prednisone |
| 4. Cortisone | 9. Prednisolone |
| 5. Cortisone acetate | 10. Clobetasol Propionate |

Nama Penganalisis (*Name of Analyst*): Assoc. Prof. Dr. Yuen Kah Hay

Tandatangan :

Pengajian/Pusat (*School /Centre*): Pusat Pengajian Sains Farmasi


Dr. YUEN KAH HAY
B. Pharm (Hons), M.Sc., Ph.D.
Associate Professor
School of Pharmaceutical Sciences
University of Science Malaysia
11800 Penang, Malaysia.

TIDAK UNTUK DIKLANKAN
NOT FOR PURPOSES OF ADVERTISEMENT



**МИНИСТЕРСТВО
ЗДРАВООХРАНЕНИЯ
РОССИЙСКОЙ ФЕДЕРАЦИИ
(МИНЗДРАВ РОССИИ)**

**ДЕПАРТАМЕНТ
ГОСУДАРСТВЕННОГО КОНТРОЛЯ КАЧЕСТВА,
ЭФФЕКТИВНОСТИ, БЕЗОПАСНОСТИ
ЛЕКАРСТВЕННЫХ СРЕДСТВ И
МЕДИЦИНСКОЙ ТЕХНИКИ**

101431, Москва, Рахмановский пер., д. 3
тел. 973-13-94, 973-18-67

16.02.2009 № 290-20/140

Генеральному директору
Фирмы "Хеминова
Интернешнл С.А."
(Испания)
г-ну Али Санта Марта

Департамент государственного контроля лекарственных средств и медицинской техники рассмотрел представленные фирмой документы на препарат СКИН-КАП, зарегистрированный в установленном порядке Минздравом России в качестве лекарственного средства для наружного применения в виде аэрозоля, крема и шампуня, подтверждающие отсутствие в составе препарата кортикостероида клобетазола.

Представленные фирмой при регистрации в Минздраве России в 1995 и 1998гг. официальные документы на препарат СКИН-КАП, результаты клинических испытаний в ведущих лечебных учреждениях России, заключения по составу из 8 стран с описанием методов исследований, а также заключение Института государственного контроля Научного центра экспертизы и государственного контроля лекарственных средств Минздрава России свидетельствуют об отсутствии в препарате клобетазола. Департамент считает, что эффективность и безопасность препарата СКИН-КАП позволяет использовать его при лечении псориаза, дерматитов и др. заболеваний кожи в соответствии с инструкцией по медицинскому применению.

Руководитель Департамента

Р.У.Хабриев

Исп. Колесникова Г.Н.
973-1635

• **Russia (translation)**

Ministry of Health of the Federation of Russia

The State department for the control of quality, efficiency, safety of medicines and medical equipment.

The State department for the control of medical products examined the documents of the product Skin-Cap, which is registered according to the norms of the Ministry of Health of Russia. The examination included the preparation of the product for external use in Spray form, cream and shampoo. This examination confirmed the absence in the product of corticosteroids clobetazol.

Official documents presented by the company to the Ministry of Health of Russia between 1995-98 combined with clinical studies by major medical centers in Russia, along with the conclusions presented by 8 countries with descriptions of their methodology and analyses including the conclusion of the State Institute of Scientific Peritaje of the Central State Ministry of Health of Russia, confirm the absence of the composition Clobetazol.

The department confirmed the effectiveness and the complete safety of the product Skin-Cap allows its use to treat psoriasis, dermatitis and other maladies of the skin used according to medical instruction.

Chief of the department

Dr. Mr. Khabriev

• Perú

MINISTERIO DE SALUD
Dirección General de Medicamentos,
Isomeros y Drogas

Lima, 12.4 MAY. 1998

DIGEMID/DEPI-OFICIO N° 483 98

Señor
Representante Legal
DROGUERIA CHEMINOVA PERU S.A.
Prolongación Iquitos N° 2261
LINCE
Presente.-

Att. R.F. Regente

Me dirijo a Ud., en relación al producto SKIN-CAP SPRAY USO TOPICO x 100 mL lote N° L-21, pesquisado según Acta N° 334-97.

Al respecto, se le comunica que el Centro Nacional de Control de Calidad del Instituto Nacional de Salud, ha emitido el Protocolo de Análisis N° 775D-P/98-CNCC-INS, de fecha 14 de Enero de 1998.


Sobre el particular, se ha verificado en la Dirección de Registros de Productos Farmacéuticos, que el mencionado lote del producto: SKIN-CAP SPRAY USO TOPICO cumple con las especificaciones técnicas autorizadas en su Registro Sanitario.

Sin otro particular,

Quedo de Ud.

Atentamente.

MINISTERIO DE SALUD
DIRECCION GENERAL DE MEDICAMENTOS,
ISOMEROS Y DROGAS


Q.F. Dra. ELVIRA TINCOPA ORTIZ
Directora Ejecutiva de Pesquisa
e Inspecciones

Nova Química Internacional S. A.
RECEPCION
Fecha: <u>24/5/98</u> Lima 10:40
Firma: 

ETO/RRH/ICHW/LRE/gdp.
c.c.: Dirección de Registros.

Archivo : CONFO.REG

• U.S.A.

MICHIGAN STATE UNIVERSITY

DEPARTMENT OF BIOCHEMISTRY
BIOCHEMISTRY BUILDING

EAST LANSING • MICHIGAN • 48824-1319 • U.S.A.

FAX: 1 (517) 353-0311

PHONE: 1 (517) 353-1600

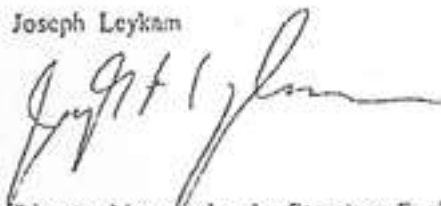
September 5, 1997

Roger Howard
Great Lakes Pharmaceuticals
Marshall Michigan

Dear Mr. Howard

As per your extraction conditions, Lot I-17 was extracted and tested by Fast Atom Bombardment Mass Spectroscopy (FAB-MS). The sample(SKIN-CAP) exhibited no clobetasol propionate in the spectra. The spectra showed the absence of the 467 M+H peak that is the molecular ion for clobetasol propionate. The 541 2M+H peak is the dimer of isopropyl myristate as demonstrated by the B/E link scan. This dimer peak may not exist in solution but may well be an artifact generated by the FAB-MS. The 271 M+H peak is the base molecular weight for isopropyl myristate. The 481M+H peak and the 407 M+H peak are unknowns. A sample of clobetasol propionate was run as a standard. The sensitivity of this mass spectrum is 1 nmole applied to the probe tip or about .5µg.

Joseph Leykam



Director Macromolecular Structure Facility

MICHIGAN STATE UNIVERSITY

DEPARTMENT OF BIOCHEMISTRY
BIOCHEMISTRY BUILDING

EAST LANSING • MICHIGAN • 48824-1319 • USA
FAX: 1 (517) 353-9334
PHONE: 1 (517) 353-1600


September 5, 1997

Roger Howard
Great Lakes Pharmaceuticals
Marshall Michigan

Dear Mr. Howard

As per your extraction conditions, Lot I-20 was extracted and tested by Fast Atom Bombardment Mass Spectroscopy (FAB-MS). The extracted sample(SKIN-CAP) exhibited no signal for clobetasol propionate in the spectra. That is the spectra showed the absence of the 467 M+H peak that is the molecular ion for clobetasol propionate. The 541 2M+H peak is the dimer of isopropyl myristate as demonstrated by the B/E link scan. This dimer peak may not exist in solution but may well be an artifact generated by the FAB-MS. The 271 M+H peak is the base molecular weight for isopropyl myristate. The 481M+H peak, the 407 M+H and the 422 M+H peak are unknowns. A sample of clobetasol propionate was run as a standard. The sensitivity of this mass spectrum is 1 pmole applied to the probe tip or about .5µg.

Joseph Leykam



Director Macromolecular Structure Facility

ANALYST WORKSHEET		1. PRODUCT BOROZIN SKIN CAP SPRAY		2. SAMPLE NUMBER I216827	
3. SEALS <input type="checkbox"/> INTACT <input checked="" type="checkbox"/> NONE <input type="checkbox"/> BROKEN		4. DATE REC'D 19-JUL-99	5. RECEIVED FROM JAMES BROWER	6. DISTRICT OR LABORATORY DDA-STL (HFD-920)	
7. DESCRIPTION OF SAMPLE One brown paper bag (with no official seal) identified as "I216827 5/20/99 MB" which contained a box labeled in part "Skin-Cap Spray 100 ml, Cheminova Internacional, Lot N-4, Exp. MAR 04" and identified as "F11-1711712-9 1-1 LAB: Sample #: I216827 DATE/INI: 5/20/99 MB". The box contained a spray can labeled in part "Skin-Cap Spray 100 ml" and identified in the same manner as the box.					
8. NET CONTENTS	<input type="checkbox"/> NOT APPLICABLE <input checked="" type="checkbox"/> NOT DETERMINED ____ UNITS EXAMINED	DECLARE/UNIT AMOUNT FOUND % of DECLARED	9. LABELING	<input checked="" type="checkbox"/> ORIGINAL(S) SUBMITTED <input checked="" type="checkbox"/> COPIES SUBMITTED <input type="checkbox"/> NONE	
10. SUMMARY OF ANALYSIS No corticosteroids were detected in the sample.					
11. RESERVE SAMPLE One box which contained an opened spray can identified "I-216827 7-20-99 JCR" in the original brown paper bag officially sealed and identified "I216827 6-12-00 John C. Reepmeyer".					
12. a. ANALYST SIGNATURE (Broke Seal <input type="checkbox"/>) (<i>μ: official seal</i>) <i>John C Reepmeyer</i>			13. WORK-SHEET CHECK	a. BY <i>J.F. Brower</i> b. DATE <i>6-15-00</i>	
b.			14. DATE REPORTED <i>6-15-00</i>		
c.			PAGE 1 OF 6		

ANALYST DATA SHEET	PRODUCT BOROZIN SKIN CAP SPRAY	SAMPLE NUMBER I216827
<p>7-20-99 Screen for corticosteroids by HPLC with rapid-scanning UV detection</p> <p>Buffer (0.1M citrate, pH 4, in saturated NaCl) – To 100 ml saturated NaCl, add 1.92 g anhydrous citric acid and adjust to pH 4 with 50% NaOH.</p> <p>Red Dye Solution – Prepare a solution of Ponceau 3R (FD&C Red No. 1) in water at a concentration of 1 mg / ml.</p> <p>Steroid Standard Solution: Dissolve 10 mg of each of the following selected corticosteroids in 100 ml EtOAc:</p> <ul style="list-style-type: none"> Triamcinolone (TRI, DDA# S-631) Hydrocortisone (HC, DDA# S-277B) Triamcinolone Acetonide (TRA, DDA# S-633C) Fluocinonide (FCAA, DDA# S-799) Clobetasol Propionate (CP, DDA# 74167B) Betamethasone Dipropionate (BMD, DDA# S-56) Triamcinolone Hexacetonide (TRH, DDA# S-634) Deoxycorticosterone Pivalate (DCP, DDA# S-159) <p>Steroid Standard Solution for HPLC – Evaporate 500 µl of Steroid Standard Solution and dissolve the residue in 300 µl methanol.</p> <p>Extraction method — Spray 25 ml of the sample into a chilled 50-ml Erlenmeyer flask. Weigh 1 g of the spray into a chilled test tube (16 x 125 mm) with a Teflon-lined cap, add 5 ml buffer and 10 ml EtOAc. For a spiked sample, add 5 ml buffer, 9.5 ml EtOAc, and 0.5 ml Steroid Standard Solution. Shake vigorously by hand to ensure that no large clumps adhere to the tube. Lay the tube on its side and mix on an oscillating shaker for 20 minutes. Add 2 drops of Red Dye Solution and mix. The dye imparts a red color in the lower aqueous layer and enables easy visualization of the 2-layer interface. Centrifuge. Separate and dry the EtOAc solution over anhydrous sodium sulfate, then evaporate to dryness. Dissolve the residue in a biphasic mixture of 10 ml heptane and 5 ml MeCN-water (9:1). Separate the lower MeCN-water layer, extract the heptane with 2 ml MeCN-water (9:1), and combine this with the first portion. Evaporate the MeCN-water to dryness. Add 300 µl MeOH to the residue, wash thoroughly, and filter through a 0.45 µm Nylon-66 micro-spin centrifuge filter (Alltech Associates, Inc.).</p> <p style="margin-left: 40px;"><u>Weight</u></p> <p style="margin-left: 80px;">NOT SPIKED: 1.0050 g</p> <p style="margin-left: 80px;">SPIKED: 0.9990 g</p> <p style="text-align: right; margin-right: 50px;"><i>JTB</i> 6-15-01</p>		
ANALYST(S) JOHN C. REEPMAYER <i>John C Reepmeyer</i>	ANALYST NO. 571	PAGE 2 OF 6 PAGES

ANALYST DATA SHEET	PRODUCT BOROZIN SKIN CAP SPRAY	SAMPLE NUMBER I216827
7-21-99 Screen for Corticosteroids, continued		
HPLC Method		
Instrumentation: Spectra Physics Liquid Chromatograph -- SP8800 pump, SP8880 autosampler, SpectraFOCUS forward optical scanning detector, Compaq Deskpro XL 5100 computer, PC1000 ver 3.0.1		
Column: Waters Symmetry C18, 75 x 4.6 mm, 3.5 µm (DDA# 772) Guard Column: BrownLee NewGuard RP-18, 15 x 3 mm, 3.5 µm Mobile Phase System #1: linear gradient 18-82% acetonitrile over 12 minutes Mobile Phase System #2: linear gradient 38-88% methanol over 12 minutes		
Gradient Delay Volume: 2.5 ml. The Spectra Physics chromatographic system gradient delay volume is 4.5 ml. Thus, the initial mobile phase conditions (18% MeCN for system #1 or 38% MeOH for system #2) will be maintained for the first 2 minutes, and the gradient is actually run from 2 to 14 min.		
Flow Rate: 1 ml/min Wavelength: Scan 200-350 nm, monitor at 240 nm Injection volume: 5 µL		
Results		
There were no peaks in the chromatograms of the MeCN-water and MeOH-water gradients that had UV spectra typical of corticosteroids.		
See Attachments A1-A12 for chromatograms and B1-B3 for UV spectra.		
Conclusion		
No corticosteroid was detected.		
<i>JFB</i> <i>6-15-00</i>		
ANALYST(S) John C. Reepmeyer <i>John C. Reepmeyer</i>	ANALYST NO. 571	PAGE 3 OF 6 PAGES

• F.D.A. 4

ANALYST DATA SHEET	PRODUCT BOROZIN SKIN CAP SPRAY	SAMPLE NUMBER I216827
7-26-99 Screen for Corticosteroids, continued		
Additional Extraction		
<p>The methanol sample solution used for HPLC was evaporated to dryness. The residue was extracted with 2 portions of 2-ml ether and filtered through a plug of filter paper. The ether was evaporated and the residue dried under high vacuum at 40°C for 1 hour. The residue was dissolved in 300 µL methanol and filtered. The sample was analyzed by the same HPLC method as before.</p>		
<p>Steroid Standard Solution: Dissolve < 1 mg (not weighed) of each of the following corticosteroids in 1.5 ml methanol.</p>		
<p>Betamethasone Dipropionate (BMD, DDA# S-56) Beclomethasone Dipropionate (BCD, DDA# S-45) Hydrocortisone Cypionate (HCC, DDA# U-551A) Triamcinolone Hexacetonide (TRH, DDA# S-634)</p>		
Results		
<p>The results are similar to the results of the previous HPLC experiment except that some peaks were less intense suggesting that these are somewhat volatile components which were removed under high vacuum or components that were poorly soluble in ether. There is no evidence for corticosteroids.</p>		
<p>See Attachments C1-C10 for chromatograms.</p>		
<p><i>JCB</i> <i>6-15-10</i></p>		
ANALYST(S) John C. Reepmeyer <i>John C Reepmeyer</i>	ANALYST NO. 571	PAGE 4 OF 6 PAGES

ANALYST DATA SHEET	PRODUCT BOROZIN SKIN CAP SPRAY	SAMPLE NUMBER I216827
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6-6-00 Silica Gel Thin-Layer Chromatography (TLC)

Silica Gel HLF (Analtech, Inc., 75 Blue Hen Drive, Newark, DE; catalog no. 47521)
Used 2.5 x 10 cm plates.

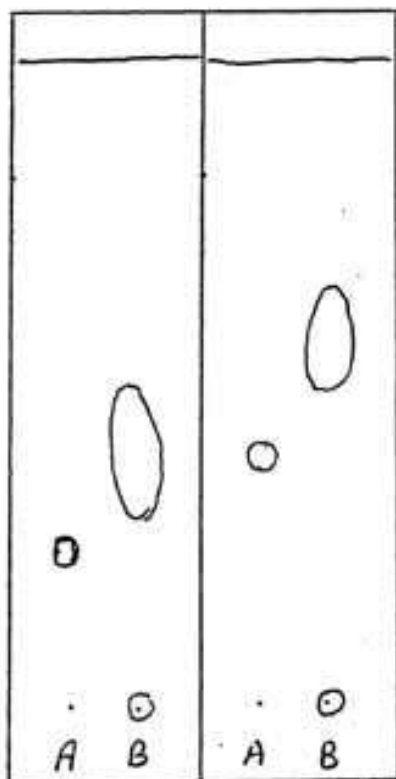
Standard: Spot an ethyl acetate solution of betamethasone 17-propionate 21-stearate on the plate.

Sample: The methanol solution of the sample used for HPLC, which had been stored in a refrigerator, was evaporated to dryness, dissolved in a small amount of ethyl acetate, and spotted on the plate.

Mobile solvent: diethyl ether – heptane (3:1)

Detection: UV hand lamp, 254 nm

Results – One spot at the origin and one fast eluting spot did not correspond to the standard.



A = betamethasone - 17-propionate - 21-stearate standard

B = Sample I 216827 extract

↑
same plate developed a second time in the same solvent.

JFB
6-15-00

ANALYST(S) John C. Reepmeyer <i>John C Reepmeyer</i>	ANALYST NO. 571	PAGE 5 OF 6 PAGES
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• F.D.A. 6

ANALYST DATA SHEET	PRODUCT BOROZIN SKIN CAP SPRAY	SAMPLE NUMBER I216827
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6-9-00 HPLC of sample extract and BMPS

Sample: The EtOAc solution of the sample (6-6-00) was evaporated and the residue was dissolved in 200 µl MeOH.

Standard: Betamethasone 17-propionate 21-stearate (BMPS) in MeOH.

Instrumentation:

Hewlett Packard 1100 HPLC with HP 1100 Quaternary Pump (G1311A), HP 1100 Vacuum Degasser (G1322A), HP 1100 Thermostatted Column Compartment (G1316A), Automatic Liquid Sampler (G1313A), HP 1100 Diode Array Detector (G1315A)

LC Conditions:

Column: Waters Symmetry C18, 75 x 4.6 mm, 3.5 µm (DDA# 772)

Guard Column: BrownLee NewGuard RP-18, 15 x 3.2 mm, 7 µm

Column Temp: 25°C

Mobile Phase: 100% MeOH isocratic

Stop Time 10 min, Post Time Off

Flow Rate: 0.6 ml/min; Max 150 bar

Wavelength: monitor at 240 nm (bandpass = 4)

Injection volume: 3 µL

Results: There was no peak corresponding to BMPS. See attachment D.

JFB
6-15-00

ANALYST(S) John C. Reepmeyer <i>John C Reepmeyer</i>	ANALYST NO. 571	PAGE 6 OF 6 PAGES
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