azierta

science to business

CLIOQUINOL
(IODOCHLORHYDROXYQUINOLINE)
PDE
DETERMINATION STRATEGY
VER. 1.0

[redacted]

EUROTOX
CORPORATE PROGRAM

TABLE OF CONTENT

1. BASIC INFORMATION

Company name:	[redacted]
Company Address:	[redacted]
Expert name:	[redacted]
Signature:	
Version:	1.0
Date:	24/03/2020
Assessment review data:	March 2020
Expiration date:	March 2025
Chemical name:	5-chloro-7-iodoquinolin-8-ol
Drug Product:	Clioquinol (iodochlorhydroxyquinoline) (oral, topical)

AZIERTA Contract Scientific support Consulting, S.L.
R. M. de Madrid, Tomo 24.326, Folio 172, Sección 8, Hoja M-437435. CIF: B-85125334
Vía de las Dos Castillas 33, Edificio 7. 28224. Pozuelo de Alarcón | Madrid
www.azierta.com | **info@azierta.com** | +34 912 771 076

REVISION NUM. (version)	TITLE	APPROVAL DATE	REVISION DESCRIPTION
01 (1.0)	Clioquinol (iodochlorhydroxyquinoline) (oral, topical): PDE determination strategy.	March 2020	First issue

AZIERTA Contract Scientific support Consulting, S.L.
R. M. de Madrid, Tomo 24.326, Folio 172, Sección 8, Hoja M-437435. CIF: B-85125334
Vía de las Dos Castillas 33, Edificio 7. 28224. Pozuelo de Alarcón | Madrid
www.azierta.com | **info@azierta.com** | +34 912 771 076

2. HAZARDS IDENTIFIED

	Yes	No	Unknown
Genotoxicant	[redacted]	[redacted]	[redacted]
Reproductive developmental toxicant	[redacted]	[redacted]	[redacted]
Carcinogen	[redacted]	[redacted]	[redacted]
Highly sensitizing potential	[redacted]	[redacted]	[redacted]

*[redacted]

**[redacted]

*** [redacted]

3. SUMMARY OF ASSESSMENT PROCESS (CALCULATION OF PDE VALUE)

PDE value (oral, topical)	[redacted] mg/day

HAZARD IDENTIFICATION	
Pharmacodynamic data	Clioquinol is a broad-spectrum antibacterial with antifungal properties. Application of clioquinol to extensive or eroded areas of the skin may lead to increased protein-bound iodine (PBI) levels within 1 week.
Acute toxicity	Acute toxicity values for clioquinol were summarized in table 1.
Repeat-dose toxicity	Repeated dose (oral) toxicity studies were conducted in rats [redacted]. The effects observed in rats were [redacted], characterized as essentially [redacted]
Carcinogenicity	Clioquinol (iodochlorhydroxyquinoline) is not listed as carcinogen by the IARC. No carcinogenicity studies were reported for clioquinol (iodochlorhydroxyquinoline) in the available literature.
"*In vitro*"/"*in vivo*" genotoxicity studies	[redacted] results were obtained form *in vitro* genotoxicity study (Ames test). [redacted] *in vivo*

	genotoxicity studies [redacted]
Reproductive/developmental toxicity	Several reproductive and developmental studies conducted in rats revealed [redacted]

IDENTIFICATION OF CRITICAL EFFECTS	
Most sensitive indicator of an adverse effect seen in non-clinical toxicity data	In conclusion [redacted]
Clinical therapeutic and adverse effects	Iodochlorhydroxyquinoline is an antibacterial agent, prescribed for dermatophytosis, mycosis barbae, seborrhoeic dermatitis, infected eczema, furunculosis and pityriasis versicolor (athlete's foot). Blistering, itching, redness, peeling, dryness, allergic skin rashes and presence of other signs of hypersensitivity were seen as adverse effects.

Point of departure	[redacted] mg/kg/day

APPLICATION OF ADJUSTMENT FACTORS		
F1: Extrapolation between species (2-12)		*A factor (values between 2 and 12) to account for extrapolation between species to human.* *This factor takes into account the comparative surface area: body weight ratios for the species concerned and for man*
F2: Inter-individual variability (10)		*A value of F2= 10 is conventionally used to allow for differences between individuals in the human population.*
F3: Toxicological study chronic or acute (1-10). Not included genotoxicity, carcinogenicity, neurotoxicity and teratogenicity		*This factor varies depending on the length of the study from which the point of departure has been selected*
F4: For severe toxicity (1-10)		*A variable factor is applied considering the potential intrinsic toxicity of the molecule within the studies.* *It may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity*
F5: NOAEL vs LOAEL **(10 if LOAEL)**		*A variable factor, up to 10, applied to results in which a NOAEL/NOAEL has not been established, the PDE being derived from a LOAEL*

PK CORRECTION	[redacted]

4. IDENTITY OF THE ACTIVE SUBSTANCE

Clioquinol (iodochlorhydroxyquinoline)

Synonyms: 5-21-03-00294 (Beilstein Handbook Reference), 5-Chlor-7-jod-8-hydroxy-chinolin, 5-Chlor-7-jod-8-hydroxy-chinolin [German], 5-Chloro-7-iodo-8-hydroxyquinoline, 5-Chloro-7-iodo-8-quinolinol, 5-Chloro-8-hydroxy-7-iodoquinoline, 7-Iodo-5-chloro-8-hydroxyquinoline, 7-Iodo-5-chloroxine, AI3-16451, Ala-Quin, Alchloquin, Alioform, Amebil, Amoenol, Bactol, Barquinol, BRN 0153637, Budoform, Caswell No. 193, CCRIS 6050, Chinoform, Chinoformum, Chloro-8-hydroxyiodoquinoline, Chloroiodoquin, Chloroiodoquine, Chlorojodochin, Cifoform, Cliochinolo, Cliochinolo [DCIT], Cliochinolum, Clioquinol, Clioquinolum, Clioquinolum [INN-Latin], Cliquinol, Corque, Cort-Quin, Cortin, Cremo-quin, Dermaform, Dioquinol, Domeform, Domeform-HC, EC 204-984-4, Eczecidin, EINECS 204-984-4, Emaform, Enteritan, Entero-bio form, Entero-Bioform, Entero-vioform, Entero-Vioformio, Enteroquinol, Enteroseptol, Enterovalodon, Enterozol, Enterseptol, Enterum locorten, Entrokin, EPA Pesticide Chemical Code 024001, HI-Enterol, HSDB 6843, Hydriodide-enterol, Hysone, Iodenterol, Iodochlorhydroxyquin, Iodochlorhydroxyquin Cream, Iodochlorhydroxyquinol, Iodochlorhydroxyquinoline, Iodochlorohydroxyquin, Iodochlorohydroxyquinoline, Iodochloroquine, Iodochloroxine, Iodochloroxychinolinum, Iodochloroxyquinoline, Iodoenterol, Iodoxyquinoline, Jodchloroxychinolinum, Lekosept, Mycoquin, Nioform, NSC 3531, NSC 74938, Oralcer, Quin-O-Crème, Quinambicide, Quinoform, Quinoform (antiseptic), Quinoform (VAN), Quinoline, chloro-8-hydroxyiodo-, Rheaform, Rheaform Boluses, Rheaform Boluses (Veterinary), Rometin, UAD Lotion, UNII-7BHQ856EJ5, Vioform, Vioform N.N.R., Vioform-Hydrocortisone, Vioform-Hydrocortisone Mild.

Chemical Abstracts Service (CAS) Registry Number: 130-26-7.

Chemical Description and Physical Properties: log P (octanol-water): 3.470, Atmospheric OH Rate Constant: 1.06E-11 cm3/molecule-sec.

Molecular formula: C9-H5-Cl-I-N-O.

Molecular weight: 305.4975 g/mol.

Melting point: 178.5 ºC.

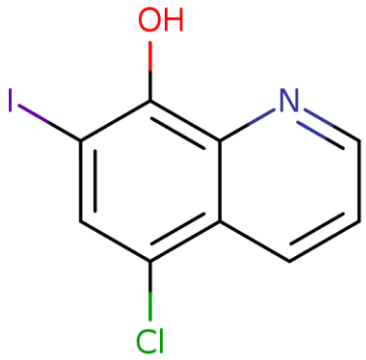

Figure 1. Structure of clioquinol (iodochlorhydroxyquinoline) (ChemIDPlus, 2020)

5. OBJECTIVE AND SEARCH STRATEGY

In accordance with the "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" (EMA/CHMP/CVMP/SWP/169430/2012) the determination of health based exposure limits for a residual active substance is based on the calculation of the Permitted Daily Exposure (PDE). Determination of a PDE involves (i) hazard identification by reviewing all relevant data, (ii) identification of "critical effects", (iii) determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects, and (iv) use of several adjustment factors to account for various uncertainties.

The NOAEL/NOEL/LOAEL/LOEL value has been used to calculate a PDE in this study.

It is the purpose of this document to provide a brief summary of the scientific information relative to clioquinol (iodochlorhydroxyquinoline) compound.

With this aim, several pharmaceutical and medical databases were scanned to reduce the risk of some reports missing. They include databases such as Pubmed, PubChem, Toxline, Drugdex, RTECS (Registry of Toxic Effects of Chemical Substances), NTP (National Toxicology Programm), CPDB (Carcinogenic Potency Database), Classification by the monograph of IARC (monograph on the evaluation of carcinogenic risk to human, International Agency for Research on Cancer monograph), DART (Development and Reproductive Database), HSDB (Hazardous Substance Data Bank) and data from medical agencies such as AEMPS (Agencia Española de Medicamentos y Productos Sanitarios), CIMA (Centro de Información on-line de medicamentos), EMA (European Medicinal Agency), FDA (Food and Drug Administration) and ECHA (European Chemical Agency). In addition, the reference book Goodman and Gilman (2006) was also consulted. The searched terms were [redacted]

13. EXPIRATION DATE: RISK ASSESSMENT

A risk assessment has been performed following the ICHQ9 "*Quality Risk Management*" to establish the expiration periods for the PDE reports considering the associated risk. The criteria for the assessment are described below:

Risk Factor	Value	Characteristics
EMA *List of medicines under additional monitoring EMA/245297/2013 Rev.75*	1	Not present
	2	Present*
PDE value	1	Higher than 1µg/day
	2	Equal/Lower than 1µg/day
	2	PDE = TTC

**The substance appears in the EMA list (EMA/245297/2013 Rev.75) alone or in combination.*

RPN = 1 (not listed in EMA/245297/2013 Rev.75) + 1 (PDE higher than 1 µg/day) = 2

Considering these criteria, the *Risk Priority Number* (RPN), which establishes the expiration date for each document, is calculated as follows:

Risk	Assessment
Low (2)	Expired in 5 years
High (3-4)	Expired in 3 years

As **RPN** = 2, expiration date 5 years.