

## 1.1. Overview of reports on clioquinol – an update

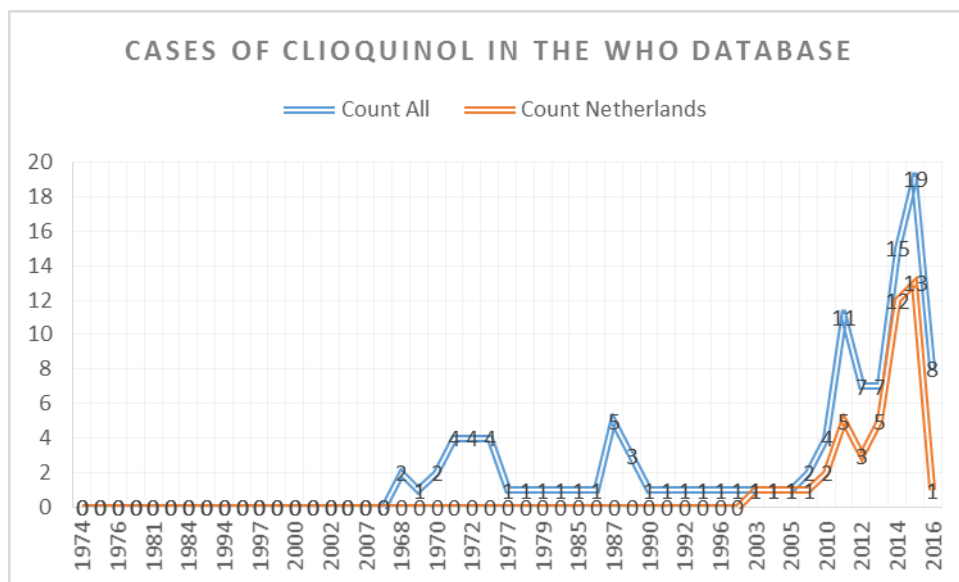
### Introduction

Clioquinol was introduced as oral treatment for *amoebiasis* in 1929. In the 1950s the indication was extended to *prevention and treatment of diarrhoea* which led to increased use of clioquinol and therefore more exposure in the population. By the end of the 1960s the first reports from Japan about subacute-myelo-optic-neuropathy (SMON) associated with the use of clioquinol appeared. The first symptoms of SMON are gastrointestinal complaints followed by neurological symptoms. Neurological symptoms only appeared if a total dose of 10-50 gram clioquinol was administered and have not been seen after a 10-day-course with a daily dose of 750mg. Also outside Japan cases of SMON were reported. Many countries, including the Netherlands, banned clioquinol for systemic use and in 1985 all oral formulations of clioquinol were worldwide taken of the market by Ciba-Geigy [1-3].

In the Netherlands, clioquinol for systemic use is no longer registered through the Medicines Evaluation Board. Therefore it is currently only available as a compounded drug. It is used for *amoebiasis and infections with dientamoeba fragilis*. To prevent accumulation of clioquinol, it is advised for adults not to use more than 750mg clioquinol per day for more than 10 consecutive days with a maximum of three courses a year. Between each course the interval should be at least two months [4-6].

In 2015 the Netherlands Pharmacovigilance Centre Lareb informed the Dutch Medicines Evaluation Board (CBG) and the Dutch Health Care Inspectorate (IGZ) about all reports concerning clioquinol with a general overview [7]. The sum of reports in 2011, 2012 and 2013 was 11 reports, while in 2014 alone Lareb received 12 reports. The number of reports in 2015 was 9 and 2 reports were received in 2016 until 13-04-2016. In December 2015 a new report was received on amnesia associated with the use of clioquinol, being the trigger report for a new analysis, which includes a more detailed view of the cases of clioquinol in the worldwide ADR database of the Uppsala Monitoring Centre (UMC), WHO Collaborating Centre for international drug monitoring. When looking at the reporting pattern over time, it can be seen that the majority of new cases on clioquinol originates from the Netherlands.

Fig 1: overview of reports concerning clioquinol in the WHO-database [8]



On 13 April 2016, the database of the Uppsala Monitoring Centre contained 113 case reports on clioquinol. 68 cases concerned females and 43 males, gender was unknown in 2 cases. Of the cases 11 originated from the Americas, 27 from Asia, 70 from Europe and 5 from Oceania. Looking at the cases from Europe in more detail, the majority originates from the Netherlands.

Table 1: Reports of clioquinol from Europe in the WHO database [8]

Country	Number of reports	Percentage
Austria	1	1.4
Belgium	1	1.4
Denmark	4	5.7
France	2	2.9
Germany	4	5.7
Netherlands	45	64.3
Poland	1	1.4
Sweden	8	11.4
United Kingdom	4	5.7

## Reports

The previous Lareb report listed 33 reports concerning adverse drug reactions associated with the systemic use of clioquinol received between 1 February 2001 until 31 December 2014 [7]. Reports on clioquinol received from 01-01-2015 until 26-04-2016 are presented below.

Table 1: Reports on clioquinol in the Larebdatabase from 01-01-2015 until 26-04-2016

Patient, Number, Sex, age, source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
A, 194621, F, 2-4 years, Specialist doctor	clioquinol susp oraal 100mg/ml, 3DD 90 mg, Infection parasitic		hyperacusis, disturbance in attention (at school), photophobia	10 Days, course given for 10 days, Recovered/resolved after 5 months
B, 198340, M, 11-20 years, Pharmacist	clioquinol (strength unknown), 3DD 3,5 ml, Amoebiasis	immunoglobuline normaal infvlst 50mg/ml, immunoglobuline normaal infvlst 50mg/ml	eye irritation	4 Days, Drug withdrawn, Recovered/resolved
C, 200926, M, 31-40 years, Pharmacist	clioquinol susp oraal 100mg/ml, 2 DD 2,5 ml, Drug use for unknown indication, nystatine susp oraal 100.000e/ml, 3DD 1DF Drug use for unknown indication	budesonide nasal 50ug/do	rash	21 Days, Unknown, Unknown
D, 202372, M, 71 years and older year, Pharmacist	clioquinol capsule 250mg, 3DD 1 DF, Drug use for unknown indication	sildenafil	dysuria	1 Day, course given for 10 days, Recovered/resolved
E, 202268, F, 5-7 years, Pharmacist	clioquinol susp oraal 100mg/ml, 1DD 1,1 ml, Amoebiasis		abdominal pain, listless, affect lability	3 Days, Drug withdrawn, Recovering/resolving
F, 207969, M, 8-10 years, Consumer	clioquinol susp oraal 100mg/ml, 3 DD 1,3 ml, Amoebiasis		headache, abdominal pain, dizziness, dyspnoea	3 Days, Drug withdrawn, Recovering/resolving
G 208094, F, 21-30 years, Consumer	clioquinol susp oraal 100mg/ml, 3DD 2,5 ml, Amoebiasis		gastric ulcer, abdominal discomfort, condition aggravated, thyroid disorder	3 days, course taken for ten days, Recovering/resolving

H, 209936, F, 11-20 years, Consumer	clioquinol susp oraal 100mg/ml, 3DD 2,5 ml, Amoebiasis	depression, suicide attempt, psychotic disorder	6 Weeks, Dose not changed, Recovered/resolved with sequel
I, 211086, F, 71 years and older, Specialist doctor	clioquinol susp oraal 100mg/ml, 2 DD 2,5 ml, Infection parasitic	amnesia	1 Day, Drug withdrawn, Recovered/resolved
J, 212216, F, 21-30 years, Consumer	clioquinol susp oraal 100mg/ml, 3DD 2,5 ml Infection parasitic, acenocoumarol 1mg, OD, Aortic valve replacement	international normalised ratio decreased (from 2.1 to 1.4) ,drug interaction	Day, Drug withdrawn, Recovering/resolving (INR 2,0 4 days after finishing course)
K, 216879, M, 2-4, year, Consumer	clioquinol susp oraal 100mg/ml, 8 ml, 3 keer per Day, 1 dosering, Infection parasitic	urinary incontinence, enuresis	3 Days, the dose for acenocoumarol was increased, the dose for clioquinol was not changed, Recovering/resolving

Patient D (202372) has an impaired renal function (no laboratory values known).

In patient E (202268) recently a slightly elevated blood thyroid stimulating hormone (TSH) was measured.

Patient G (208094) also had Graves' disease in the past.

Additional information concerning report H (209936): This serious (Disabling) spontaneous report from a consumer concerns a female aged 11-20 years, with psychosis, suicide attempt and depression following administration of clioquinol for amoebiasis with a latency of 52 days after start. On 03-04-2013 Clioquinol 100ml 10 days 3 x 2,50 ml/day was prescribed. On 15-05-2013 a second course clioquinol 100ml 7 days 3 x 2,25 ml/day prescribed (but not the whole course was taken, unknown how many days clioquinol was used). On 25/26-05-2013 the patient had suicidal ideation, heard voices, psychosis. On 28-05-2013 a third course of clioquinol 100ml 7 days 3 x 2,25 ml/day was prescribed. In August 2013 Dientamoeba fragilis a fourth course of clioquinol 100ml 7 days 3 x 2,5 ml/day was prescribed together with mebendazole. In June 2013, the patient was also prescribed vaginal miconazolenitrate (Gyno-Daktarin®) for vaginal candidiasis and in July 2013 itraconazole for 'vaginal complaints'. The patient is still treated for depression (2 years after onset) with sertraline and zopiclone to prevent a recurrence. She is unable to attend school due to a lack of energy. Concomitant medication was not reported. Before the psychosis occurred the patient had suffered from unexplained medical complaints for a year and had been seen by a pediatrician in 2012. In June 2015 chronic Lyme's disease was diagnosed. Due to a fall, the patient was seen by a neurologist. An MRI did not show any abnormalities.

Additional information concerning report I (211086): This non-serious spontaneous report from a specialist doctor concerns a female aged 71 years and older years, with amnesia following administration of clioquinol for dientamoeba fragilis infection with a latency of 1 day after start. Clioquinol was administered in the afternoon and in the evening, dosage was 2 times 250 mg. In the morning the patient woke up in a confused state. She was disorientated and was not able to remember several things, like the name of her doctor and the indication for clioquinol. The drug clioquinol was withdrawn. The patient recovered within several hours. The symptoms disappeared during the afternoon. No neurologic deficit was seen. Concomitant medication was not reported. The medical history indicates that the patient had breast carcinoma (2014). The patient has no known past drug therapy.

Concerning this latter case of amnesia; Lareb received 1 additional report concerning amnesia and one of a confusional state associated with the systemic use of clioquinol. These were both prescribed in the previous overview.

Report 53425 (described in overview 2015)

This non-serious spontaneous report from a pharmacist concerns a female aged 41-50 years, with amnesia following administration of clioquinol 100 mg/ml 3 dd 250 mg for dientamoeba fragilis with a latency of 8 days after start and 1 day after withdrawal of clioquinol. The patient was recovering two days after the start of the reaction. Concomitant medication was doxycycline (startdate unknown).

Report 51228 (described in overview 2015)

This non-serious spontaneous report from a general practitioner concerns a male aged 41-50 years years, with pale skin and acute confusional state following administration of clioquinol 100 mg/ml for infection parasitic with a latency of 1 day after start. The patient experienced disorientation in time, place and person. He had no insight into his own complaints. There was no motoric failure. The drug clioquinol was withdrawn. The patient outcome is unknown as the report was submitted immediately following the reaction and no follow-up information was later received. Concomitant medications were thiamazole, levothyroxine sodium. The patient has no known medical history. The patient has no known past drug therapy.

### Other sources of information

#### *SmPC*

Because clioquinol is no longer registered through the Dutch Medicines Evaluation Board, a Summary of Product Characteristics (SmPC) is not available. There is a leaflet available of the clioquinol oral suspension which is provided by Apotheek De Magistrale Bereider, one of the large compounding pharmacies in the Netherlands. Both the leaflet and the Farmacotherapeutisch Kompas describe that intake of a cumulative dose of 10-50 gram can lead to subacute-myelo-optico-neuropathy. Symptoms are abdominal pain and diarrhoea followed by sensomotoric disturbance. Also visual disturbances and blindness can occur [5,6]. The Informatorium Medicamentorum and Kinderformularium mention only the risks of SMON when using a cumulative dose of 10-50 gram clioquinol after oral administration [9,10].

#### *Literature*

Neurotoxicity and SMON associated with the systemic use of clioquinol have been described in various articles [11-18]. Neurological symptoms, such as paresthesia and visual disturbance, are due to degeneration of the long fibres of the spinal cord and the optic nerve [1]. Neurological symptoms only appeared if a total dose of 10-50 gram clioquinol was administered. If a daily dose of 600mg was used neurological symptoms would occur after 48.8 days on average, and twice as fast if the daily dose was doubled. Neurological symptoms have not been reported after a 10-day-course with a daily dose of 750 mg [1,3]. In addition, cases of acute encephalopathy similar to classic transient global amnesia (TGA) have been described after the intake of mostly large doses of clioquinol [19-23]. The clioquinol-type of TGA is characterized by an insidious start in cases mostly younger than those affected by the classic type. Patients were not able to retain what was shown or said to them, while they were otherwise able to act apparently normally and even to execute complex activities. During the acute amnesic episode, which could last up to 3 days (longer than in the classic type), there was also a retrograde amnesia, which could extend over months or years. After the episode of TGA, the capability to retain impressions returned and the retrograde amnesic gap was filled again. In both the classic and the clioquinol-type only the acute episode remained 'blank' [19-22]. With regards to the amnesia, a solid mechanism has not been described in the past. Selective cerebral lesions have been demonstrated in laboratory mice after high dosages of clioquinol [22,23]. Ferrier described two cases of acute encephalopathy and epilepsy of delayed onset after ingestion of high dosages of clioquinol [23]. More recent studies have looked at the chelation of synaptic zinc as a possible culprit of amnesia caused by clioquinol [24,25]. Ismail et al. found a pattern of cell loss reminiscent of that seen in models of temporal lobe epilepsy in mice injected with clioquinol [24]. Takeda et al. found indications that acute exposure to clioquinol impairs long-term (24 h) memory in the hippocampus of young rats [25].

#### *Prescription data*

Table 2. Number of patients using clioquinol in the Netherlands between 2009 and 2014 [26]

Drug	2009	2010	2011	2012	2013	2014
Clioquinol	3,732	4,330	5,484	6,968	8,621	7,779

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb has previously written an overview of reported ADRs for clioquinol which included 16 reports of neurological symptoms associated with the use of clioquinol [7]. In 2015 and 2016 Lareb has received 11 new cases on clioquinol concerning various

ADRs, including a new case of amnesia. Cases of acute amnesia have been described for clioquinol, albeit mostly for high dosages, although Mumenthaler et al. reported on an acute amnesic episodes in 3 patients using a therapeutic dosage of clioquinol with a latency of about 24 hours [21]. This is similar to the cases Lareb presents here. The exact mechanism by which clioquinol could impair memory has not been elucidated, recent studies have looked at clioquinol's potential to chelate synaptic zinc as a possible culprit [24,25]. One new serious case (209936) has been reported concerning psychosis, suicide attempt and depression. However, due to the patient's medical history it is difficult to draw a firm conclusion on causality for this case.

Prescription data show that the amount of clioquinol users in the Netherlands has doubled over the past 5 years, although 2014 showed a slight drop in users compared to 2013. The number of users for 2015 isn't available yet. Looking at the number of ADR reports in the Worldwide database of the UMC, it can be seen that a majority of reports on clioquinol reported in the last years stems from the Netherlands.

Lareb wants to inform the Dutch Medicines Evaluation Board and Health Care Inspectorate about these new findings.

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