Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Norfloxacin

NL/W/0040/pdWS/001

Rapporteur:	The Netherlands
Finalisation procedure (day 90):	11 September 2016

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Senro capsulas
INN (or common name) of the active substance(s):	Norfloxacin
MAH (s):	MADAUS, S.A., Spain
Pharmaco-therapeutic group (ATC Code):	JO1MA06
Pharmaceutical form(s) and strength(s):	capsules 400 mg

LIST OF ABBREVIATIONS

EMA	European Medicines Agency
MAH	Marketing Authorisation Holder
PL	Package Leaflet
SE	Standard Error
SmPC	Summary of Product Characteristics

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in section 4.5 and 2.

Summary of outcome

- ☐ No change
- ☐ Change: addition of wording
- ☐ New study data
- ☒ New information regarding cyclosporin/norfloxacin interaction in SmPC section 4.5
- ☐ Paediatric information clarified:
- ☐ New indication

II. RECOMMENDATION

Based on the paediatric data published the Member States have agreed that the product information of norfloxacin containing products should include information on the interaction between norfloxacin and cyclosporin in the SmPC and PL.

SmPC section 4.5
Cyclosporin
Elevated serum levels of cyclosporin have been reported with concomitant use of norfloxacin. Cyclosporin serum concentrations should therefore be monitored and the dosage adjusted as appropriate.

PL section 2 - 'Other medicines and X'
Tell your doctor or pharmacist if you take:
- cyclosporin (used to prevent rejection of organ transplants)

III. INTRODUCTION

In 2008, one MAH in Spain (MADAUS, S.A.) submitted one publication of a completed paediatric study for norfloxacin: 'Norfloxacin interferes with cyclosporine disposition in pediatric patients undergoing renal transplantation' (McLellan et al, 1995).

Consequently, norfloxacin has been included in the 18th wave of the Worksharing according to Article 45 of the Paediatric Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use, with the Netherlands as Rapporteur.

However, when the MAH was contacted in 2013 with the request to submit the paediatric study for norfloxacin, it was established that the concerned product Senro capsulas is no longer on the market, and that the MAH no longer exists. Consequently, no critical expert overview was provided, no statement with regard to the benefit/risk was made nor on potential regulatory action, and no proposals for the product information were submitted. Nevertheless, it has been agreed with the EMA to initiate a Paediatric Worksharing procedure without MAH participation, and present the assessment of the published paediatric study in this report.

The originator product in the Netherlands, Noroxin, is no longer registered as it was withdrawn in 2013. However, four generic products, film-coated tablets containing 400 mg norfloxacin are still registered in the Netherlands, of which two are registered through MRP (NL/H/1573/001 and DE/H/0173/001).

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study

Not applicable.

IV.2 Non-clinical aspects

As with other quinolones, norfloxacin caused arthropathy in immature animals. Preclinical studies conducted in Beagle dogs demonstrated damage to articular cartilage in weight-bearing joints. Based on the results of animal tests, damage to joint cartilage in the growing body can not entirely be ruled out.

IV.3 Clinical aspects

1. Introduction

The safety of use and the place of therapy for fluoroquinolones in paediatrics[1]
The preclinical finding of articular cartilage damage limits the general use of fluoroquinolones in paediatric patients due to the concern that similar effects (e.g. damage to growth plate cartilage) might occur in children. Case reports of tendinitis and tendon rupture have also been reported in association with fluoroquinolone use. Literature reveals contradictory results with regard to adverse events observed with fluoroquinolone use in children. The calculated risk for tendon or joint disorders was found to be no different in the children treated with fluoroquinolones (ofloxacin, levofloxacin and ciprofloxacin) when compared to those prescribed azithromycin (Chuen et al, 2002[2]). Musculoskeletal adverse events were more frequently associated with pefloxacin (18.2%) than ciprofloxacin (3.3%) (Chalumeau M, 2003[3]), and musculoskeletal events (arthritis, arthralgias, tendinopathy, gait abnormality) within sixty days of starting therapy were higher in levofloxacin-treated children when compared with those treated with non-fluoroquinolone antibiotics (Noel GJ, 2007[4]). Other relatively rare but serious toxicities have been associated with fluoroquinolone use, including prolonged QT interval, photosensitivity and acute liver failure. The frequency of their occurrence in children can only be inferred from spontaneous reports of the use in adults.

Despite these concerns of possible adverse effects, fluoroquinolones are used in infants and children in specific clinical settings where their properties are felt by the prescriber to outweigh potential risks for drug-associated adverse events. Examples include pulmonary exacerbations in patients with cystic fibrosis, infections associated with complicated urogenital anomalies, immunosuppressed patients, those with infectious diarrheal diseases and patients who develop infections secondary to multi-drug resistant organisms (i.e. *Shigella* species, *Salmonella*

[1] Jennifer A. Goldman and Gregory L. Kearns. Fluoroquinolone Use in Paediatrics: Focus on Safety and Place in Therapy.
WHO 18th Expert Committee on the Selection and Use of Essential Medicines (2011)

[2] Chuen YL et al. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. Pediatr Infect Dis J 2002;21:525-9

[3] Chalumeau M et al. Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Pediatrics 2003;111;e714-e719

[4] Noel GJ et al. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. Pediatr Infect Dis J 2007;26:879-891

species, *Vibrio cholerae*, *Campylobacter jejuni)*, *Bacillus anthracis*, mycobacteria and *Pseudomonas aeruginosa*.

The place of norfloxacin between other fluoroquinolones
Since the antibacterial spectrum of norfloxacin is generally less active than ciprofloxacin and other newer fluoroquinolones, the practical applicability of norfloxacin is more limited than that of ciprofloxacin. It is currently used primarily to treat infections associated with the gastrointestinal or genitourinary systems.
Norfloxacin is registered in many EU countries. In the Netherlands it is only available as film-coated tablets containing 400 mg norfloxacin that are indicated for the use in adult patients only, in the treatment of upper and lower complicated and uncomplicated, acute and chronic urinary tract infections (except for complicated pyelonephritis) and urinary tract infections associated with urologic surgery and nephrolithiasis. The use of norfloxacin is contraindicated in prepubertal children and growing adolescents in the Netherlands and several other countries.

2. Clinical study

Title*: Roman A. McLellan, Robert K. Drobitch, D. Heather McLellan, Philip D. Acott, John F. S. Crocker and Kenneth W. Renton. Norfloxacin interferes with cyclosporine disposition in pediatric patients undergoing renal transplantation; Clin. Pharmacol. Ther. 1995 Sep. 58(3): 322-327*

➢ Description

This concerns a retrospective, controlled open label study aiming to evaluate the interaction between norfloxacin and cyclosporin in paediatric kidney transplant patients.
The study was performed in the Department of Pharmacology, Dalhousie University, Canada and the Department of Pediatrics, Izaak Walton Killam Hospital for Children, Canada.

➢ Methods

- Objective(s)

To determine, retrospectively, factors that may have accounted for a reduction in daily cyclosporin doses in paediatric patients who underwent kidney transplantation, based on the likelihood that concomitant prophylactic use of norfloxacin may have reduced cyclosporin clearance through inhibition of the cytochrome P450 isozyme.

- Study design

Open label trial. Retrospective analysis in paediatric patients who underwent kidney transplantation, 2-year period.

- Study population/Sample size

Eleven paediatric patients (aged 6 – 12 years) who underwent kidney transplantation.

- Treatments

General medication
All kidney transplant recipients were treated with a standardized medication protocol both during and after surgery: cortisol sodium succinate (500 mg/m IV), antilymphocyte globulin (1 A/10 kg),

antihistamines, azathioprine (2 mg/kg orally) and prednisone (1 mg/kg orally). All patients in both groups received verapamil and clonidine.

Cyclosporin

Cyclosporin administration was started on day 10 by continuous intravenous infusion (3 mg/kg/day) with the dose and interval being adjusted to produce blood levels of 150 to 400 ng/ml. All dosage adjustments were made by the attending physician in response to routine blood level measurements of cyclosporin. After 24 to 48 hours of intravenous administration, oral cyclosporin doses (10 mg/kg/day) were given 3 times daily.

Norfloxacin

Five patients received norfloxacin orally once daily (5 to 10 mg/kg) throughout the period of the study. Two of the patients received norfloxacin before transplantation, and three were started on average 23 days after transplantation. The other six patients did not receive norfloxacin.

- Outcomes/endpoints

- Cyclosporin clearance reduction in daily cyclosporin doses in paediatric patients who underwent kidney transplantation on the basis of concomitant prophylactic use of norfloxacin.
- The effect of norfloxacin on specific drug-metabolizing cytochrome P450 3A4 isozymes *in vitro* in human liver microsomes.
- The effect of norfloxacin in rat liver microsomes on the activity of cytochrome P450 3A2, the isozyme responsible for cyclosporin metabolism in this species, and on the activity of the rat cytochrome P450 isozymes lA, 2E1, and 4A1.

- Statistical Methods

All data are shown as mean (± SE) values. The groups were compared by an unpaired *t* test, with a value of $p < 0.05$ considered to be significant.

➢ Results

- Recruitment/Number analysed/Baseline data

Table I. Characterization of patient groups

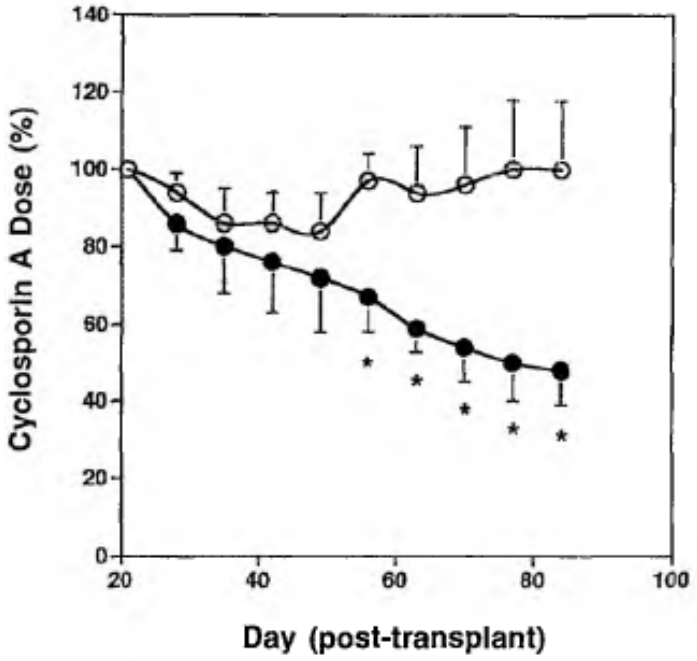
	Control group	*Norfloxacin group*
No. of patients	6	5
Mean age at transplantation (yr)	10 ± 2	8 ± 2
Male/female ratio	4/2	2/3
Mean body surface area (m^2)	1.07 ± 0.16	1.23 ± 0.32
Mean hospitalization time (days)	99 ± 20	105 ± 11

- Efficacy results

The authors conclude that norfloxacin therapy was very effective in the studied paediatric population, however, on which results this conclusion was based is not clear. On the basis of these very small numbers of patients no conclusions with regard to efficacy can be drawn. The objective of this study was, however, not to prove efficacy of norfloxacin but to determine whether norfloxacin decreases the clearance of cyclosporin through inhibition of cytochrome P450 isozyme responsible for the metabolism of cyclosporin.

It was observed that patients who received norfloxacin required a lower mean daily cyclosporin dose on discharge from the hospital (4.5 ± 1.0 mg/kg/day; range 1.8 to 7.9 mg/kg/day) compared with patients who did not receive norfloxacin (7.4 ± 1.8 mg/kg/day; range 4.5 to 15.0 mg/kg/day). These doses were necessary to maintain 12-hour trough cyclosporin blood levels of 150 to 400 ng/ml, which is the normal clinical target in paediatric kidney transplant recipients. In the group of patients who did not receive norfloxacin, the dose of cyclosporin remained stable for at least 84 days after transplantation. In the group treated with norfloxacin, the dose of cyclosporin decreased gradually up to 84 days after transplantation and the mean dose was significantly lower after day 49 (Figure 1). The cyclosporin dose was calculated with reference to 21 days after transplantation, because at this time most patients were stable in their daily dosing regimens. Cyclosporin doses were calculated as daily cyclosporin dose each patient received divided by day-21 post transplant dose.

Figure 1 Cyclosporin dose-time profiles

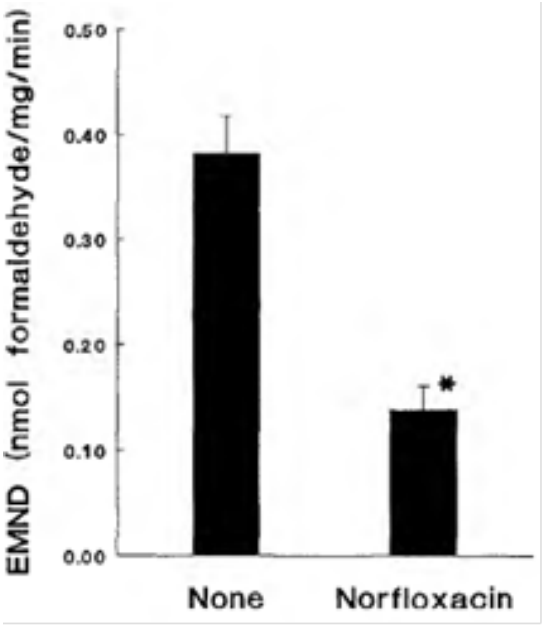


Cyclosporin dose-time profiles of:
patients receiving cyclosporin (open circles)
patients receiving cyclosporin and norfloxacin (closed circles)
Individual *points* represent means of patient groups; *bars* represent SE.

There was significant difference (*p < 0.05) between the two patient groups 49 days after transplantation. Difference between the groups could not be explained by patient characteristics (table 1), nor by administered medicines to either group (see text ‘General medication’, page 8).

Human microsomal isozyme activity was determined in a hepatic fraction prepared from a 55-year old woman who had a high CYP3A activity. In this human liver microsomal fraction, norfloxacin inhibited the metabolism of erythromycin by CYP3A4, the isozyme that carries out cyclosporin metabolism, by approximately 64% (Figure 2).

Figure 2 Effect of norfloxacin on erythromycin-*N*-demethylation *(EMND)* activity in human hepatic microsomes



Each bar represents mean ± SE of four separate incubations with human hepatic microsome fraction.

In presence of norfloxacin, EMND activity was decreased significantly (*p < 0.01) by approximately 64%.

Rat microsomal enzyme activities were determined *in vitro* and used to evaluate various drug metabolizing P450 isozymes. In each case, individual isozyme activities were increased significantly when the animals were pretreated with specific inducers compared with uninduced control animals. The addition of norfloxacin did not inhibit the normal or induced metabolism of ethoxyresorufin (CYP1A), *para*-nitrophenol (CYP2E1), and lauric acid (CYP4A1). The metabolism of erythromycin by CYP3A2, which is the isozyme responsible for cyclosporin metabolism in the male rat, was significantly depressed by norfloxacin in both the induced (40%) and uninduced (78%) animals.

- Safety results

From the sparse information on safety no firm conclusions can be drawn with regard of the safety of the use of norfloxacin in this particular population of children who underwent kidney transplantation. Norfloxacin was well tolerated in these children, with only one patient exhibiting an arthralgia and rash that subsided without discontinuation of norfloxacin. There were no episodes of organ rejection in both the norfloxacin and control groups. All patients observed in both groups had normal kidney function during the study period.
No serious or new safety issues were reported that would necessitate any adjustments of the SmPC.

3. Discussion on clinical aspects and conclusion

The authors conclude that the results strongly suggest that norfloxacin inhibits the metabolic clearance of cyclosporin in children, most likely through inhibition of cytochrome P450 3A4. Thus patients receiving cyclosporin and fluoroquinolone antibiotics, such as norfloxacin, must be monitored closely to maintain levels within the target range for effective immunosuppression, and for the prevention of adverse side effects such as nephrotoxicity.

The authors' conclusions are endorsed. The article of McLellan was published in 1995. The interaction between norfloxacin and cyclosporin has been scientifically confirmed since. The approved SmPC of norfloxacin in the Netherlands and many other Member States includes a statement regarding this interaction in section 4.5, stating that cyclosporin serum concentrations should be monitored and the dosage adjusted as appropriate.

This warning is considered adequate. However, it is not included in the product information of norfloxacin products in all Member States. The agreed wording should be included in the SmPC and PL by means of a variation.

The limited information in the article of McLellan 1995 on paediatric kidney transplant patients does not lead to any other new insights. Kinetics in this particular paediatric population are essentially the same as in adult patients. No serious or new safety issues in children were reported that would necessitate any other adjustments of the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Based on the paediatric data published, the Member States have agreed that the product information of norfloxacin containing products should include information on the interaction between norfloxacin and cyclosporin in SmPC section 4.5 and PL section 2.

- **Recommendation**

The following information should be included in section 4.5 of the SmPC of norfloxacin containing products:

Cyclosporin
Elevated serum levels of cyclosporin have been reported with concomitant use of norfloxacin. Cyclosporin serum concentrations should therefore be monitored and the dosage adjusted as appropriate.

Consequently, in PL section 2 under 'Other medicines and X', the following wording should be stated:
Tell your doctor or pharmacist if you take:
- cyclosporin (used to prevent rejection of organ transplants)

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Not applicable; no MAHs were involved in this Worksharing procedure.