

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205352Orig1s000**

**ENVIRONMENTAL ASSESSMENT**

## **Finding of No Significant Impact**

**NDA 205-352**

**Aleve® PM (naproxen sodium, diphenhydramine HCl) Tablets**

### **Food and Drug Administration Center for Drug Evaluation and Research**

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

Bayer HealthCare, Consumer Care requests approval of NDA 205-352 Aleve® PM (naproxen sodium, diphenhydramine HCl) Tablets for the relief of occasional sleeplessness when associated with minor aches and pains. In support of its application, Bayer HealthCare prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impact of approval of this application.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact due to approval of this application and has concluded that this action is not expected to have a significant impact on the environment. Therefore, an environmental impact statement will not be prepared.

Attachment: May 2012, Environmental Assessment



Drug substances: Naproxen sodium; Diphenhydramine

**Environmental Assessment (EA)**

Status: May 2012

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4 May 2012

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June 5<sup>th</sup>, 2012



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**1. Date**

The environmental assessment report for naproxen sodium was originally prepared on Feb 12, 2010. This report is updated to account for the addition of diphenhydramine in the formulation.

**2. Name of Applicant**

The name of the applicant submitting the environmental assessment is Bayer HealthCare, Consumer Care.

**3. Address**

The address of the applicant is

36 Columbia Road  
P.O. Box 1910  
Morristown, N.J. 07962-1910

**4. Description of proposed action**

## a) Requested action

Bayer HealthCare, Consumer Care, has filed a new drug application (NDA) pursuant to Section 505 (b) of the Federal Food, Drug, and Cosmetic Act for naproxen sodium coated tablet 220 mg + diphenhydramine HCl 25 mg, a formulation for the relief of occasional sleeplessness when associated with minor aches and pains with the active ingredients naproxen sodium and diphenhydramine. An environmental assessment is required following CFR Part 25, since the action limit for the categorical exclusion regarding the expected introduction concentration for naproxen is exceeded (see [chapter 5](#)), while for diphenhydramine it is calculated to be below the threshold level.

It will be packaged in a foil/polyester laminate pouch (2 count), and in CR HDPE bottles (20, 40, and 80 count).

## b) Need for action

Naproxen sodium/diphenhydramine will be used as an over-the-counter medication in humans for the the relief of occasional sleeplessness when associated with minor aches and pains.

## c) Location of use

Naproxen sodium/diphenhydramine primarily will be used in patients' homes and to some extent in hospitals and clinics throughout the United States.

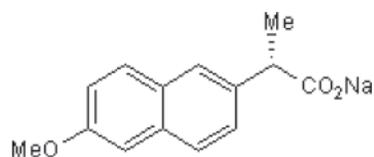
## d) Disposal site

No special method of disposal of waste by the end user is anticipated. United States' hospitals, pharmacies or clinics will dispose of empty or partially empty packages in accordance with applicable local, state and federal regulations. In home, empty or partially emptied containers will be disposed off by domestic solid waste, which will be incinerated or disposed off in landfills.

**5. Identification of substances that are subject of the proposed action**

Naproxen sodium is a well-established and effective Nonsteroidal Anti-Inflammatory Drug (NSAID) approved for Over-The-Counter (OTC) use.

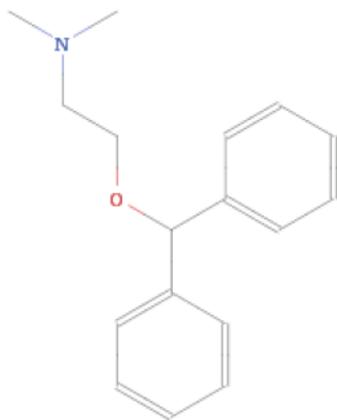
<b>CAS No</b>	26159-34-2
<b>IUPAC name</b>	(-)-6-methoxy-alpha-methyl-2-naphthalene-acetic acid, sodium salt
<b>INN</b>	Naproxen sodium
<b>Molecular mass</b>	252.24
<b>Molecular formula</b>	C <sub>14</sub> H <sub>13</sub> NaO <sub>3</sub>

**Structural formula:**


Diphenhydramine, is a well-established OTC active ingredient. Diphenhydramine is sedating and belongs to the monoethanolamine group of antihistamines.

## Diphenhydramine

<b>CAS No</b>	147-24-0
<b>IUPAC name</b>	2-(diphenylmethoxy)-N,N-dimethylethanamine
<b>INN</b>	Diphenhydramine
<b>Molecular mass</b>	255.355 g/mol
<b>Molecular formula</b>	C <sub>17</sub> H <sub>21</sub> NO

**Structural formula:**

1 tablet Naproxen sodium/diphenhydramine contains:

- 220 mg naproxen sodium, 25 mg diphenhydramine
- Excipients: microcrystalline cellulose, povidone, purified water, talc, magnesium stearate, hypromellose 2910, titanium dioxide, FD&C blue #2 aluminum lake, polyethylene glycol 8000

**6. Environmental issues****6.1 Naproxene****6.1.1 Fate of emitted substance into the environment**

Naproxen is almost exclusively excreted in urine in the form of conjugates of naproxen, (I =70 %), and a hydroxylated metabolite (II=28 %) (1). The excreted soluble conjugates (ie. glucuronides), hydrolyze readily (2), (3).

There are three reasons why the major product, I, is the only chemical that may have an environmental impact. First, it is the major component excreted following product use. Second, microbial adaptation to I will also extend to II (4), because conjugates are easily cleaved to the parent compound by microorganisms. Third, the rate of microbial metabolism of II should be faster than I (4) as this metabolite is more polar than the parent compound. Naproxen will exist in solution in media of environmental interest (between pH 5 and 9) as the salt form owing to a low pKa value. Sanitary waste treatment systems are operated as close to 6.5 as possible in order to promote rapid organism growth. Significant inhibition occurs at both higher and lower pH values (5). The distribution of I into various metal salts will depend on the concentration of various cations in the aquatic environment. The salt content of North American river waters is

largely due to four cationic and four anionic species. The concentrations of the four cations, Na, K, Ca, and Mg, decrease (6) in the order  $Ca > Na > Mg > K$ . The corresponding naproxen salts of these cations are all very soluble (7). Consequently, the sodium or potassium salts are used as surrogates for naproxen in most environmental fate and effects studies.

### 6.1.2 Physico-chemical characterisation

In Table 1, the physico-chemical properties which are descriptive in terms of the environmental fate of naproxen sodium extended release tablet, 660 mg or its drug substance naproxen sodium (as naproxen) are summarized.

**Table 1: Selected physico-chemical data of naproxen**

Parameter	Value and conditions	Method <sup>1)</sup>	Source
Water solubility	0.12 g/L (pH4) 12 g/L (pH7) 196 g/L (pH9)20°C	--	Chowhan (7)
Dissociation constant (pKa)	4.15-4.6	--	Report ref. no. 1; Unger (8)
Photolysis estimated environmental half-lives in aqueous solutions	Spring: 0.163 d summer: 0.134 d fall: 0.283 d winter: 0.483 d (pH 6.96)	FDA TAD 3.10	Report ref. no. 2
Vapour pressure Henry's Law constant	$5.0 \times 10^{-9}$ Torr, $<10^{-7}$ atm m <sup>3</sup> /mol (pH 4, 7, and 9)	--	Report ref. no. 3
n-Octanol/Water partition coefficient (Pow) (log Pow)	254-307 (2.40-2.49)(pH4) 5.53-5.99 (0.74-0.78) (pH7) 0.163-0.170 (-0.788- -0.770)(pH9)	FDA TAD 3.02	Report ref. no. 4

1) FDA TAD = US Federal Drug Agency Technical Assistance Document no., Technical Assistant Handbook, US Dept. of Commerce, NTIS Springfield, VA, 1987

Only a very small fraction of naproxen remains in solution in the free acid form when solutions are at a pH of environmental interest (0.003 % at pH 9, 0.3 % at pH 7, and 22 % at pH 5).

### 6.1.3 Environmental depletion mechanisms

Preliminary studies of the photoreaction of naproxen sodium in an aqueous solution at pH 5, 7, and 9 were performed as outlined in protocol FDA TAD 3.10 Photodegradation. The test chemical degraded very rapidly when exposed to sunlight with half-lives of 15 to 35 minutes. The major photoproducts were identified as 6-methoxy-1-naphthalene ethanone and 6-methoxy-2-naphthylene ethanol. The alcohol photoproduct is photoreactive in solution and had a half-life

from 1.75 to 8.13 hours. The alcohol photoproduct also accelerated the photolysis of naproxen sodium, and to avoid this interference in the definitive measurements, the starting naproxen sodium concentrations were kept at a minimum consistent with quantitation of the residual, unphotolyzed compound. Both photoproducts are transient intermediates, and undergo additional photoreaction (see Report ref. no. 2).

Isidori et al. (9) reported similar metabolites in a study, where naproxen sodium was introduced in drinking water and irradiated at room temperature for 72 hours by a solar simulation Xenon lamp. Additionally to the ketone and the alcohol, an ether and a dimer derivative were identified. Half-lives were not given.

An investigation of the biodegradability of naproxen and other pharmaceutical products was reported in the literature (3). However, the report did not provide a description of the test method nor indicate the level of test compound used in each biodegradation test. The source and level of organisms used in the biodegradation test, as well as the concentration of test chemical, can affect the rate of biotransformation. Reference to the literature indicated that naturally occurring organisms of the genus *Pseudomonas* are able to degrade naphthalenic (10) and other aromatic compounds (4), (11).

A preliminary study was undertaken at Syntex Research, Inc., to select a source of naturally occurring organisms from media from a domestic waste water treatment facility that would have the capability of using naproxen as a food source. This study was performed by the Department of Analytical and Environmental Research. Tests were conducted at 3.3 ppm organic carbon (5.0 ppm naproxen sodium) according to procedures used in the "modified Zahn-Wellens Test" (12). Three *Pseudomonas* species, *paucimobilis*, *maltophilia*, and *putida*, that were able to use naproxen as a sole source of carbon and energy.

Preliminary tests used secondary effluent, mixed liquor suspended solids (MLSS) and activated sludge as test media. They were all obtained from a domestic waste treatment facility. There was a significant light industrial component in the influent to this plant. Solutions of naproxen sodium in these media were aerated for 15 days. Biotransformation of naproxen sodium was monitored by analysis of filtrates from the test suspensions, since naproxen sodium is not adsorbed to sludge solids. No significant biodegradation took place in clarified MLSS. In contrast, there was no naproxen sodium left in MLSS by day 7, or in the activated sludge mixture by day 10. The time required to reduce the concentration of naproxen sodium by one-half in MLSS was approximately 84 hours. When the level of naproxen sodium in the initial MLTS test suspensions was decreased by 10-fold to 0.5 µg/mL, only 30 % naproxen sodium remained after one day, and there was no detectable amount in suspension after 3 days. A reduction to 30 % in one day corresponds to a half-life of approximately 13.8 hours. The rate of disappearance of naproxen suggested a first-order decay, indicative of the presence of sufficient organisms to use naproxen as a food source (12). No structurally related compounds were observed on HPLC analysis for residual naproxen, indicating that the biotransformation resulted in a breakdown of the naphthalene ring structure (see Report ref. no. 5).

A second, definitive study conducted at ABC Laboratories, Inc. determined the rate of the primary degradation and acclimatization of MLSS to naproxen sodium in media frequently encountered in publicly owned waste water treatment plants. Here also, the "modified Zahn-Wellens Test" was used as the first step for acclimation of organisms. The first acclimation of

aerated MLSS, treated with naproxen sodium at a concentration of 5 mg/L, was continued for 25 days. The biotransformation of naproxen sodium was followed by HPLC analysis. This part of the study duplicated the study discussed above. The second part of the study involved the conduct of a “closed bottle test”, studies where samples of a solution of naproxen sodium and essential minerals were inoculated with material drawn from the acclimation flask on days 0, 5, 10, and 15. Sufficient bottles were prepared so that the primary biotransformation of naproxen sodium could be followed by HPLC, and the extent of biodegradation followed by the consumption of dissolved oxygen. The third part of the study identified the organisms that were responsible for the biodegradation of naproxen sodium in the closed bottle test.

In the first acclimation part of this study, the rate of naproxen sodium biotransformation was slow at first, but increased between days 15 and 25 so that there was no material left in suspension at day 25. The closed bottle test in the second part of the study indicated that the organisms in the acclimation media became more effective over time at degrading naproxen sodium, as well as the 1:1 reference mixture of glucose/glutamic acid. A parallel loss of naproxen sodium and oxygen in the closed bottle test showed a rapid mineralization once biotransformation started.

The principal organisms identified in the incubated closed bottles were *Flavobacterium multivorum*, and *Pseudomonas putida*, as identified by the “Rapid NFY” method for microbial identification. These are the same species that use other polynuclear aromatic hydrocarbons as a food source (14). These organisms are common to soil, and to activated sludge or biological filter (trickling filter) waste water treatment processes (15). Based on the preceding information i.e. the inherent degradation in the Zahn-Wellens test and ready degradation in the closed-bottle test after adaptation, it may be concluded that salts of naproxen may biodegrade in the secondary treatment section of a waste water treatment facility. The structural similarity, but greater polarity, of the hydroxylated metabolite compared to the glucuronide indicates that the first will biodegrade at least as fast in waste treatment media (see Report ref. no. 6).

#### 6.1.4 Conclusions on environmental depletion

Naproxen sodium is not expected to partition into suspended organic material due to the low octanol/water partition coefficient (range of  $K_{OW} = 5.5-6.0$ ) at a pH 7. Naproxen sodium is expected to remain in the aquatic phase during the primary settling step of waste treatment.

When the waste stream enters the secondary treatment phase, naproxen will not be transferred from the aquatic to atmospheric phase regardless of whether secondary treatment is by the activated sludge or the trickling (biological) filter process. Transport to the atmospheric phase is not significant, as the Henrys law constant is always less than  $10^{-7} \text{ m}^3 \text{ atm/mol}$ .

Biodegradation of naproxen sodium at environmental levels is expected to follow first order kinetics (16), (17). Depletion in the course of aeration and settling phases in a waste treatment plant will vary, depending on the residence times in the aeration and settling basins.

As a “worst case” example, we assume that the total treatment time is 2 hours. Based on the rate of naproxen sodium biodegradation in studies performed to date, the concentration of naproxen sodium might not be significantly reduced in this period. Since naproxen is not absorbed to

solids from the activated sludge process, the concentration in a waste water treatment plant effluent is assumed to be the same as in the influent.

Photolysis will quickly degrade naproxen sodium if not removed by waste treatment. The longest environmental photolytic half-life, 0.483 days, occurs under winter conditions at a pH of 7. Under these conditions, a one-day photolysis would reduce the naproxen sodium concentration by 77 %. Continued photolysis would reduce the environmental concentration at a minimal rate of at least 77 % per day. It has to be stated, however, that photolysis is limited in natural waters depending on turbidity and adsorption of light in the water column. Therefore, estimated half-lives cannot be directly be used to estimate depletion rates of the test compound in natural environments.

Bioaccumulation of residual naproxen, and the transformation products, by aquatic life is not expected to occur under any circumstances, due to 1) low values for octanol/water partition coefficients at environmentally significant pH values, 2) continued photolytic activity, and 3) continued biodegradation by aquatic microorganisms identified in the biodegradation studies.

Due to the fact that the compound will remain entirely in the water phase, the environmental assessment will be restricted to the aquatic environment.

#### 6.1.5 Estimation of environmental concentrations of naproxen sodium in water

In order to account for a worst-case scenario, the amount of active ingredient is calculated as the sodium salt of naproxen. According to the marketing forecast, an amount of 987,205 kg naproxen sodium are projected to be marketed in 2017, which represents the fifth year after market approval of the NDA and includes baseline sales of other naproxen formulations (see [Annex, CBI](#)).

The expected introduction concentration (EIC) was calculated according to the following formula as given in the FDA Guidance for Industry document (18) and using the updated water consumption figure given in (19):

$$\text{EIC} = 987,205 \text{ kg} * 1/1.27 * 10^{-11} * 1/365 \text{ days} * 10^9 \text{ } \mu\text{g}/\text{kg} = \mathbf{21.30 \text{ ppb}}$$

The expected environmental concentration (EEC) can be derived from the EIC (see 1) applying a default factor of 10 for dilution in surface waters:

$$\text{EEC} = \text{EIC} / 10 = \mathbf{2.13 \text{ ppb}} \text{ or } \mathbf{2.13 \text{ } \mu\text{g}/\text{L}}$$

The trigger value for further studies is the EIC of 1 ppb or EEC of 0.1 ppb, which was exceeded by a factor of approximately 20.

#### 6.1.6 Environmental effects of naproxen sodium

Since a rapid depletion mechanism could not be identified for naproxen sodium, further testing to determine the environmental effects was performed for the substance.

### 6.1.7 Results of microbial inhibition test

In agreement with the tiered approach described in the FDA guidance document (18), a test in a microbial species was performed.

The minimum inhibitory concentrations (MIC) of naproxen sodium were determined in a study conducted by Springborn Laboratories, Inc. (see Report ref. no. 7). Where possible, organisms originating from aquatic sources were utilized, although the groups were the same as recommended in the FDA Environmental Assessment Technical Assistance Document 4.02. The following Table 2 summarizes the minimum inhibitory concentrations of naproxen sodium to the bacteria *Clostridium perfringens* and *Streptomyces fragmentans subspecies aquatica*, the mold *Aspergillus niger*, the blue green algae *Nostoc spec.*, and the fungus *Fusarium oxysporum*.

**Table 2: Minimum inhibitory concentration (MIC) of naproxen (sodium) to different microorganisms**

Species	MIC naproxen sodium [mg/L]	MIC naproxen [mg/L]
<i>Clostridium perfringens</i>	>1000	>913
<i>Streptomyces fragmentans subspecies aquatica</i>	>1000	>913
<i>Streptomyces fragmentans subspecies aquatica</i>	1000	913
<i>Nostoc spec.</i>	80	73
<i>Fusarium oxysporum</i>	400	365

### 6.1.8 Results of ecotoxicity tests for tier 1

Since a rapid depletion of naproxen disodium could not be established, acute aquatic toxicity test were performed in tier 1 following the instructions of the guidance document (18).

#### Acute immobilization test in *Daphnia magna*

The acute effects of naproxen sodium on the freshwater invertebrate water flea, *Daphnia magna*, a representative planktonic macroinvertebrate, were evaluated under static conditions in a well controlled study at ABC Laboratories, Inc. Quadruplicate groups of five *Daphnia magna* larvae, less than 24 hours old, were exposed to concentrations of naproxen sodium ranging from 0 to 560 mg/L of water (nominal) in 200 mL, static systems for 48 hours. Actual measured naproxen sodium concentrations (HPLC) were 0 to 550 mg/L. The 48-hour median effective concentration of naproxen that immobilized 50 % of the exposed daphnids. (EC<sub>50</sub>), was calculated to be 140 mg/L. The 48-hour naproxen sodium NOEC was 51 mg/L (see Report ref. no. 8).

#### Acute toxicity test in *Hyalella azteca*

The acute toxicity of naproxen sodium on the epifaunal freshwater invertebrate, *Hyalella azteca*, was determined under static conditions in a well controlled study at ABC Laboratories, Inc.

Groups of four replicates, each with 10 amphipods of approximately the same age and size, were exposed to nominal concentrations of naproxen sodium ranging from 0 to 1000 mg/L of water for 96 hours. Actual measured concentrations (by HPLC) were 0 to 1100 mg/L. The 96-hour median naproxen sodium concentration that immobilized 50 % of the exposed population, the EC<sub>50</sub>, was calculated to be 383 mg/L. The 96-hour naproxen sodium NOEC was 120 mg/L (see Report ref. no. 9).

#### Acute toxicity test in Bluegill sunfish

The acute toxicity of naproxen sodium to Bluegill (*Lepomis macrochirus*) a limnic warm-water fish was assessed in a well controlled study at ABC Laboratories, Inc. Twenty fish per group having a mean weight of  $0.78 \pm 0.21$  g were exposed for 96 hours in a flow-through system to nominal concentrations of 0 to 1000 mg/L naproxen sodium. Actual measured concentrations (by HPLC) ranged from 0 to 970 mg/L. Mortality, behavioral effects (e.g. surfacing and loss of equilibrium), and change in physiology or appearance (e.g. increased respiration and discoloration) were observed in groups exposed to 480 and 970 mg/L naproxen sodium. The naproxen sodium 96-hour LC<sub>50</sub> was calculated to be 560 mg/L. The 96-hour naproxen sodium NOEC was 240 mg/L (see Report ref. no. 10).

#### Acute toxicity test in Rainbow trout

The acute toxicity of naproxen sodium to Rainbow trout (*Oncorhynchus mykiss*), a limnic cold-water fish was assessed in a well controlled study at ABC Laboratories, Inc. Twenty fish per group having a mean weight of  $0.97 \pm 0.21$  g were exposed for 96 hours in a flow-through system to nominal naproxen sodium concentrations of 0 to 1000 mg/L. Actual measured concentrations (by HPLC) ranged from 0 to 990 mg/L. Mortality, behavioral effects (e.g. surfacing and loss of equilibrium), and changes in physiology and appearance (e.g. increased respiration and discoloration) were observed in groups exposed to 470 and 990 mg naproxen sodium/L (actual concentration). The naproxen sodium 96-hour LC<sub>50</sub> was calculated to be 690 mg/L. The 96-hour naproxen sodium NOEC was 240 mg/L (see Report ref. no. 11).

Additionally, further test results are reported by Cleuvers (19), (21) on *Daphnia* and algal toxicity of naproxen sodium (see Table 3).

In a 72-hour growth inhibition test, unicellular green algae (*Desmodesmus subspicatus*) were exposed to naproxen sodium. The EC<sub>50</sub> was higher than 320 mg/L. Further, the effects of naproxen sodium was studied in the duckweed *Lemna minor* over 7 days. The EC<sub>50</sub> was determined with 24.2 mg/L. Finally, *Daphnia magna* were exposed in an acute immobilization test to naproxen sodium. The EC<sub>50</sub> was determined with 174 mg/L.

In a further study, the EC<sub>50</sub> was determined in the green-algae *Desmodesmus subspicatus* with 625.5 mg/L after 72 hours exposure. For *Daphnia magna*, the EC<sub>50</sub> was determined in the acute immobilization test over 48 hours with 166.3 mg/L, which was in good agreement with the previous tests.

Isidori et al. (9) published results on tests with algae and invertebrates (see Table 3). The LC/EC<sub>50</sub> values for the rotifer *Brachionus calyciflorus*, the crustaceans *Thamnocephalus platyurus* and *Ceriodaphnia dubia* in acute tests were 43.5 and 54.6 mg/L, for the alga *Pseudokirchneriella subcapitata* it was determined with 39.3 mg/L for growth inhibition.

The above tests published in the literature are considered to be of lower quality than the studies initiated by the applicant, mainly because the test substance concentrations during the tests were not analytically verified. However, toxic concentrations were in good agreement and in the range of LC/EC<sub>50</sub> values determined in the tests referenced above and therefore confirmed the low aquatic toxicity of naproxen in various species. The risk assessment, i.e. the ratio of the effective concentrations and the estimated environmental levels, will be based on the high quality studies initiated by the applicant.

### 6.1.9 Risk assessment according to tiered approach

A summary of the aquatic toxicity tests is given in the following Table 3.

**Table 3: Summary of acute toxicity tests with different aquatic species (refernces)**

Species	LC <sub>50</sub> /EC <sub>50</sub> / MIC [mg/L]	NOEC [mg/L]
Microorganisms: Lowest MIC in <i>Nostoc spec.</i>	80	not determined
Green algae: <i>Desmodesmus subspicatus</i>	>320 (19) 625.5 (21)	not determined 266 (EC <sub>5</sub> ) (21)
<i>Pseudokirchneriella subcapitata</i>	39.3 (9)	not determined
Duckweed: <i>Lemna minor</i>	24.2 (19)	not determined
Crustacean invertebrate: <i>Daphnia magna</i>	140 174 (19) 166.3 (21)	51 not determined 26 (EC <sub>5</sub> ) (21)
<i>Thamnocephalus platyurus</i>	43.5 (9)	not determined
<i>Ceriodaphnia dubia</i>	43.6 (9)	not determined
<i>Hyalella azteca</i>	383	120
Rotifer: <i>Brachionus calyciflorus</i>	54.6 (9)	not determined
Fish: <i>Lepomis macrochirus</i>	560	240
<i>Onkorhynchus mykiss</i>	690	240

Tier 1 requires that the  $EC_{50}$  or  $LC_{50}$  to EIC ratio is higher than 1000 in order to stop the fate and effect testing after that step. The comparison between the lowest determined  $LC_{50}/EC_{50}$  in aquatic species, the  $EC_{50}$  of 140 mg/L in *Daphnia magna* and the EIC of 21.30  $\mu\text{g/L}$  clearly fulfills this criterion ( $>6500$ ). Even, if the lowest (analytically not verified) result of Cleavers<sup>20</sup> for the duckweed *Lemna minor* is used, the ratio  $EC_{50}$  to EIC is 1100. Since the octanol/water partition coefficient ( $\log P_{ow}$ ) was below 3.5, no further test in tier 3 is required according to the FDA guidance document (18).

#### 6.1.10 Summary of environmental effects tests

The initial assessment of microbial toxicity in the test with different microorganisms showed that naproxen sodium is not toxic to microbial communities at concentrations of  $\leq 80$  mg/L.

In the acute aquatic tests performed according to the requirements of tier 1, the  $LC_{50}/EC_{50}$  was between 140 to 690 mg/L. The ratio between the lowest  $EC_{50}$  and the EIC exceeded the assessment factor of 1000 ( $>6500$  [tier 1]). Therefore, no further testing is required.

#### 6.1.11 Overall summary

Naproxen sodium is primarily released into the aquatic environment after oral administration and subsequent excretion.

Biodegradation or other elimination pathways do not significantly contribute to a reduction of the emitted drug, however, photolysis was identified as a potential degradation pathway as well as inherent biodegradation indicated by the Zahn-Wellens test.

Due to the hydrophilic nature of the compound, a low adsorption and accumulation potential of naproxen sodium is presumed. Thus, no risks for the compartment soil or sediment are expected. The introduction of naproxen sodium into the terrestrial environment due to agricultural sewage sludge use is considered to be highly unlikely. Consequently, no terrestrial testing and assessment was performed for the compound.

The volatility of naproxen sodium is negligible, thus no atmospheric exposure or spread is expected.

The aquatic toxicity studies in tier 1 showed no indication of adverse effects at environmentally relevant concentrations. The  $EC_{50}/EIC$  trigger value (assessment factor of 1000) was exceeded by a factor of at least 6.5. These results indicate that there is no aquatic risk related to the environmental introduction of naproxen sodium.

## 6.2 Diphenhydramine

### 6.2.1 Estimation of environmental concentrations diphenhydramine in water

According to the marketing forecast, an amount of 5,460 kg diphenhydramine are projected to be marketed in 2017, which represents the fifth year after market approval of the NDA and includes baseline sales of other diphenhydramine formulations (see [Annex, CBI](#)).

The expected introduction concentration (EIC) was calculated according to the following formula as given in the FDA Guidance for Industry document (18) and using the updated water consumption figure given in (19):

$$\text{EIC} = 5,460 \text{ kg} * 1/1.27 * 10^{-11} * 1/365 \text{ days} * 10^9 \text{ } \mu\text{g}/\text{kg} = \mathbf{0.093 \text{ ppb}}$$

The expected environmental concentration (EEC) can be derived from the EIC (see 1) applying a default factor of 10 for dilution in surface waters:

$$\text{EEC} = \text{EIC} / 10 = \mathbf{0.0093 \text{ ppb}} \text{ or } \mathbf{0.0093 \text{ } \mu\text{g}/\text{L}}$$

The trigger value for further studies is the EIC of 1 ppb or EEC of 0.1 ppb, which was not exceeded.

Therefore, the active ingredient diphenhydramine is eligible for a categorical exclusion.

In accordance with 21 CFR § 25.31, a categorical exclusion from the requirement to prepare an environmental assessment for an Investigational New Drug Application is claimed.

To the best of our knowledge, no extraordinary circumstances exist that indicate the proposed action may significantly affect the quality of the human environment, as described under § 25.21.

## 7. Mitigation measures

Environmental impacts associated with the production of naproxen sodium and diphenhydramine will be avoided or mitigated by the use of appropriate control measures in accord with all federal, state, and local regulations. Air emissions control devices include vent condensers, scrubbers and fabric filter dust collectors. Environmental impacts associated with the disposition of drug substance and/or metabolites following consumption in humans will be mitigated by conventional wastewater treatment plants or septic systems. All rejected, unused or out-of-date product will be disposed by incineration or by landfill in accordance with all federal, state, and local regulatory requirements

The lack of toxicity to test organisms in the aquatic compartment, together with the extremely low mammalian toxicity and the comparable low expected environmental concentration do not indicate the need for specific mitigation measures for the drug after use in patients.

## 8. Alternatives to proposed action

No potential environmental impacts are foreseen with the use of naproxen sodium and diphenhydramine.

The FDA has two alternatives by which to respond to this proposed action: Approval of the proposed action through the issuance of a Finding of No Significant Impact (FONSI) or Non-approval and notification of intent to prepare an Environmental Impact Statement (EIS).

We believe that the first action, issuance of a FONSI, is fully justified by this Environmental Assessment. Manufacturing operations will be in compliance with the regulations of the applicable governmental agencies. Releases of naproxen sodium to the environment will be mitigated as discussed in [Section 7](#). Fate and effects testing (described in [Section 6](#)) support the position that the manufacture and use of naproxen sodium will not produce an adverse effect on the environment. Approval of the proposed action will make available to the consumer a significantly valuable, relatively safe with limited unwarranted side effects and environmentally safe drug.

**9. CV of EA expert and author**Dr. rer. nat. Reinhard **Laenge**

- 1973 – 1980:** University education in Biology  
Technical University Darmstadt (THD)  
and University of Kiel (CAU)  
Dipl.-Biol. 1980
- 1980 – 1983:** Research work in the field of marine and limnic ecosystems  
at the Institute of Oceanography, CAU, Kiel  
Dr. rer. nat., 1983
- 1983 – 1984:** Expert for Aquatic Ecology with UNESCO in Alexandria, Egypt
- 1986 - July 1990:** Work in the field of Environmental Toxicology  
in the Section Inhalation Toxicology of the Dept. (since 1983 Main  
Dept.); since 1991 for Experimental Toxicology, Schering AG,  
Berlin
- since 1. August 1990:** Head of the Laboratory Ecotoxicology, Nonclinical Drug Safety,  
Bayer Pharma AG



## 10. References

### 10.1 Literature

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## 10.2 Reports

Report no.	Title	Company	Study/Report no.
ref. no. 1	Measurement of the Dissociation Constant of Naproxen from the pH Solubility Profile (confidential)		Environmental Assessment, NDA 21-076, page 6
ref. no. 2	Photolysis of Naproxen sodium (confidential)		Environmental Assessment, NDA 21-076, page 8
ref. no. 3	Relative Volatility of Naproxen (confidential)		Environmental Assessment, NDA 21-076, page 6
ref. no. 4	n-Octanol/Water Distribution Ratio for Naproxen (confidential)		Environmental Assessment, NDA 21-076, page 6
ref. no. 5	Naproxen Environmental Fate Preliminary Assessment at Aerobic Aquatic Biodegradation (confidential)		Environmental Assessment, NDA 21-076, page 9
ref. no. 6	Aquatic Biodegradation of Naproxen Sodium (confidential)		Environmental Assessment, NDA 21-076, page 10
ref. no. 7	Naproxen Sodium-Determination of Microbial Growth Inhibition, (confidential)	Springbom Laboratories, Inc, Wareham, Mass.	Environmental Assessment, NDA 21-076, page 12
ref. no. 8	Acute Toxicity of Naproxen Sodium to <i>Daphnia magna</i> (confidential)	ABC Labs., Columbia, Missouri	Environmental Assessment, NDA 21-076, page 13
ref. no. 9	Acute Toxicity of Naproxen Sodium to <i>Hyaella azteca</i> (confidential)	ABC Labs., Columbia, Missouri	Environmental Assessment, NDA 21-076, page 13
ref. no. 10	Acute Flow-Through Toxicity of Naproxen Sodium to Bluegill ( <i>L.epomis macrochirus</i> ), (confidential)	ABC Labs., Columbia, Missouri	Environmental Assessment, NDA 21-076, page 13
ref. no. 11	Acute Flow-Through Toxicity of Naproxen Sodium to Rainbow trout ( <i>Oncorhynchus mykiss</i> ), No. 39322 (confidential)	ABC Labs., Columbia, Missouri	Environmental Assessment, NDA 21-076, page 13

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/s/  
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RAANAN A BLOOM  
05/02/2013

NAKISSA SADRIEH  
05/03/2013



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmaceutical Science/Immediate Office

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**Memorandum**

**Date:** May 02, 2013

**From:** Raanan A. Bloom, Ph.D.  
OPS/IO/SRS

**To:** Luz E. Rivera  
ONDQA

**Through:** Nakissa Sadrieh, Ph.D.  
OPS/IO/SRS

**Subject:** NDA 205-352 Aleve® PM (naproxen sodium, diphenhydramine HCl) Tablets  
Review of Environmental Assessment

**Sponsor:** Bayer HealthCare, Consumer Care

**A. Background**

Bayer HealthCare, Consumer Care, has filed a new drug application (NDA) pursuant to Section 505 (b) of the Federal Food, Drug, and Cosmetic Act for naproxen sodium coated tablet, 220 mg, plus diphenhydramine HCl, 25 mg, for the relief of occasional sleeplessness when associated with minor aches and pains. An environmental assessment (EA) has being submitted pursuant to 21 CFR part 25.

**B. Discussion**

**Executive Summary**

The submitted EA supports the NDA for naproxen sodium coated tablet, 220 mg, plus diphenhydramine HCl, 25 mg. The EA was prepared in accordance with 21 CFR Part 25 and FDA 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

The sponsor estimates an EIC of 21.30 µg naproxen sodium/L (ppb) in water, based on a use estimate of 987,205 kg in year 2015 (the highest year in the 5 year marketing forecasts) of all Bayer naproxen products used in the United States. In order to account for a worst-case scenario, the amount of active ingredient is calculated as the sodium salt of naproxen.

The sponsor provides ecotoxicology data to estimate LC50/EC50 toxicity values for naproxen. These values are compared to estimated expected introductory or environmental concentrations (EIC and MEEC) based on the predicted amount of naproxen sodium residues expected to enter the environment by year 5 after approval; the resulting ratio was determined to be significantly greater than 1000, concluding the introduction of naproxen sodium residues into the environment due to approval of this application is not expected to cause a significant environmental impact.

### C. Environmental Assessment Review

#### 1. **Date:** May 2012

The EA was originally prepared on April 23, 2009, under NDA 200-364 (Aleve® extended release tablets). The report was updated on Feb 12, 2010, to account for naproxen sodium in all Aleve® products. This report is updated to account for the addition of diphenhydramine in the formula and increased naproxen sales. No additional toxicology information is presented. Updated EIC and MEEC values are calculated. Toxicity/exposure ratios are recalculated.

**2. Applicant:** Bayer HealthCare, Consumer Care

**3. Address:** 36 Columbia Road  
P.O. Box 1910  
Morristown, N.J. 07962-1910

**4. Proposed Action:** for the relief of occasional sleeplessness when associated with minor aches and pains

#### 5. **Identification of Chemicals:**

1. Naproxen sodium is a non-steroidal anti-inflammatory drug commonly used over-the-counter for the temporary relief of minor aches and minor pain due to: minor pain of arthritis, muscular aches, backache, menstrual cramps, headache, toothache, the common cold. Temporarily it reduces fever.

CAS No: 26159-34-2

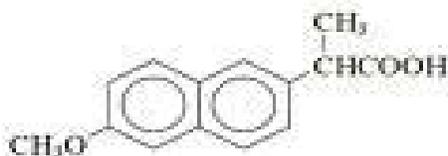
IUPAC name: (-)-6-methoxy-alpha-methyl-2-naphthalene-acetic acid, sodium salt

INN: Naproxen sodium

Molecular mass: 252.24

Molecular formula: C<sub>14</sub>H<sub>13</sub>NaO<sub>3</sub>

Structural formula:



2. Diphenhydramine HCl

CAS No: 147-24-0

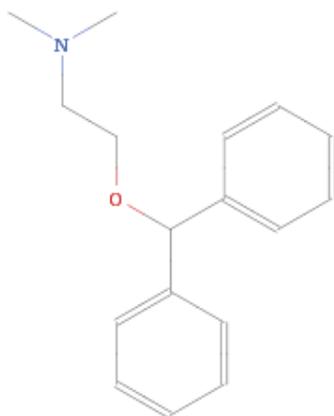
IUPAC name: 2-(diphenylmethoxy)-N,N-dimethylethanamine

INN: Diphenhydramine

Molecular mass: 255.355 g/mol

Molecular formula: C<sub>17</sub>H<sub>21</sub>NO

Structural formula:



**6. Environmental Fate Characterization**

Refer to the Feb 12, 2010 EA and EA Review (dated March 18, 2010) for NDA 200-364

**Environmental Concentrations**

The expected introduction concentration (EIC) was calculated according to FDA Guidance for Industry document using updated estimated production values.

The Maximum Expected Environmental Concentration (MEEC) is derived from the EIC by applying a default factor of 10 for dilution in surface waters.

**Naproxen sodium**

EIC = 21.30 ppb (ug/L)

MEEC = 2.13 ppb

**Diphenhydramine HCl**

EIC = 0.093 ppb

MEEC = 0.0093 ppb

The applicant requests a categorical exclusion from the requirement to prepare an environmental assessment for diphenhydramine and states, "To the best of our knowledge, no extraordinary circumstances exist that indicate the proposed action may significantly affect the quality of the human environment."

Agency action for the approval of diphenhydramine HCl is categorically excluded under 21CFR25.31b. No "extraordinary circumstances" were noted in a literature review.

## **7. Ecological Toxicity**

Refer to the Feb 12, 2010 EA and EA Review (dated March 18, 2010) for NDA 200-364 (see EA for references).

## **8. Risk Characterization**

Toxicity/exposure ratios for naproxen sodium are recalculated as follows:

The lowest determined LC50/EC50 is 140 mg/L in *Daphnia magna*. The worst-case EIC is 21.30 ug/L. The MEEC equals 2.13 ug/L.

140 mg/L / 21.30 ug/L > 6500

140 mg/L / 2.13 ug/L > 65000

This margin is sufficient to determine that no further testing is required according to FDA Guidelines. Additionally, a search of the literature (see below) did not indicate that naproxen is ecotoxic at estimated exposure concentrations. Naproxen would not be expected to accumulate due to the hydrophilic nature of naproxen (octanol/water partition coefficient is below 3.5).

## **8. Cumulative Environmental Fate and Effects**

Naproxen sodium is approved in numerous ANDAs and NDAs. IMS National Sales data provides sales value lower than those used to estimate the EIC for this risk assessment. This is partially due to the method used to calculate IMS data; in this instance naproxen (IMS) versus naproxen sodium. A cumulative assessment would not generate higher EIC values or a different risk profile.

## **9. Mitigation Measures and Alternatives**

Since no adverse environmental impact is expected, no mitigation methods are addressed.

## **10. Literature Reviewed**

Occurrence and Fate of Carbamazepine, Clofibric Acid, Diclofenac, Ibuprofen, Ketoprofen, and Naproxen in Surface Waters. Céline Tixier, Heinz P. Singer, Sjeff Oellers, and Stephan R. Müller  
Environ. Sci. Technol., 2003, 37 (6), pp 1061–1068.

Mixture toxicity of the anti-inflammatory drugs diclofenac, ibuprofen, naproxen, and acetylsalicylic acid. Michael Cleuvers . *Ecotoxicology and Environmental Safety* Volume 59, Issue 3, November 2004, Pages 309-315

Nesbitt, Richard Aug 1, 2011. Effects of chronic exposure to ibuprofen and naproxen on Florida flagfish (*Jordanella floridae*) over one complete life-cycle. Master's Thesis. <https://ir.library.dcuoit.ca/handle/10155/176>.

Berninger, Jason P. Effects of the antihistamine diphenhydramine on selected aquatic organisms *Environmental Toxicology and Chemistry* 2011 30:9 p. 2065-2072

References do not contradict findings of the EA.

## **11. Comments and Conclusions**

The comparison between the lowest determined LC50/EC50 in *Daphnia magna* is greater than 1000 (140 mg/L/ 21.30 µg/L >6500). Also, since the octanol/water partition coefficient (log Pow) was below 3.5, no further testing is indicated according to FDA guidance. Significant impacts are not expected at the EIC or MEEC..

Based on an evaluation of the information provided in this EA and previous EAs, in FDA guidance, and on the scientific validity of the “no effects” conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA.

A Finding of No Significant Impact (FONSI) is recommended.

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05/02/2013

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