DICLOFENAC SODIUM: ADE DETERMINATION STRATEGY

LAB
TABLE OF CONTENT

1. BASIC INFORMATION ............................................................................................................. 3
2. HAZARDS IDENTIFIED ......................................................................................................... 4
3. SUMMARY OF ASSESSMENT PROCESS (CALCULATION OF PDE VALUE) .............. 5
4. IDENTIFY OF THE ACTIVE SUBSTANCE ........................................................................... 8
5. OBJECTIVE AND SEARCH STRATEGY .............................................................................. 9
6. INTRODUCTION .................................................................................................................. 11
7. HAZARD IDENTIFICATION .................................................................................................. 11
   a. Pharmacodynamics data .................................................................................................. 11
   b. Acute toxicity ................................................................................................................ 12
   c. Repeat dose toxicity ...................................................................................................... 14
   d. Carcinogenicity .............................................................................................................. 15
   e. In vitro / in vivo genotoxicity studies .......................................................................... 15
   f. Reproductive and developmental toxicity ..................................................................... 16
8. IDENTIFICATION OF CRITICAL EFFECTS ...................................................................... 17
   a. Most sensitive indicator of an adverse effect seen in non-clinical toxicity data ........ 17
   b. Clinical therapeutic and adverse effects ................................................................. 17
9. RATIONAL FOR NOAEL VALUES SELECTION ................................................................. 19
10. APPLICATION OF ADJUSTMENT FACTORS (rational for the adjustment factors) .... 19
    a. UFₐ: Interspecies differences ..................................................................................... 20
    b. UFᵢᵢ: Inter-individual variability ............................................................................... 20
    c. UFₑ: Subchronic-to-Chronic Extrapolation (Duration of exposure) ......................... 20
    d. UFₑₑ: LOAEL-to-NOAEL Extrapolation .................................................................. 21
    e. UFₑₑₑ: Database Completeness ............................................................................... 21
11. MODIFYING FACTOR (MF) .................................................................................................... 21
12. PK CORRECTION ................................................................................................................ 22
13. ADE CALCULATION ............................................................................................................ 22
14. REFERENCES ....................................................................................................................... 24

ANNEX 1: PHARMACOKINETICS AND METABOLISM ............................................................. 26
ANNEX 2: SUMMARY OF THE EXPERT CV ........................................................................... 28

“Reproduction or unauthorized distribution is strictly prohibited. The present document is licensed to a “single client” or organization, and may not be re-sold, copied, or redistributed to other companies or organizations. The use by any company other than the one indicated in the watermark is prohibited. The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement”

AZIERTA Contract Scientific support Consulting, S.L.
C/ Francisco González Leal 2  PCB, C/Baldiri Reixac, 4, 4ª pl.  CM Los Ejecutivos
28233 Pozuelo de Alarcón  Of-B-8, Ed. Torre I.  Av. Pedro de Heredia Piso 3, Dpcho 307
Madrid  08028 Barcelona  Cartagena de Indias (Colombia)

R.M. de Madrid, Tomo 24.326, Folio 172, Sección 8, Hoja M-437435. CIF: B-85125334
### 1. BASIC INFORMATION

<table>
<thead>
<tr>
<th>Company name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Company address:</td>
<td></td>
</tr>
<tr>
<td>Expert name:</td>
<td></td>
</tr>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Assessment review data:</td>
<td></td>
</tr>
<tr>
<td>Chemical name:</td>
<td>sodium;2-[2-(2,6-dichloroanilino) phenyl] acetat</td>
</tr>
<tr>
<td>Drug product:</td>
<td>Diclofenac sodium (oral)</td>
</tr>
</tbody>
</table>
## 2. HAZARDS IDENTIFIED

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotoxicant</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Reproductive developmental toxicant</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Carcinogen</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Highly sensitizing potential</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

“The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement.”

AZIERTA Contract Scientific support Consulting, S.L.

C/ Francisco González Leal 2
28233 Pozuelo de Alarcón
Madrid

PCB, C/Baldiri Reixac, 4, 4ª pl.
Of. B-8, Ed. Torre l.
08028 Barcelona

CM Los Ejecutivos
Av. Pedro de Heredia Piso 3, Dpho 307
Cartagena de Indias (Colombia)

R.M. de Madrid, Tomo 24.326, Folio 172, Sección 8, Hoja M-437435. CIF: B-85125334
3. SUMMARY OF ASSESSMENT PROCESS (CALCULATION OF PDE VALUE)

| ADE value | 0.25 mg/day |

### HAZARD IDENTIFICATION

#### Pharmacodynamics data

The antiinflammatory effects of diclofenac are believed to be due to inhibition of both leukocyte migration and the enzyme cylooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis is responsible for the analgesic effects of diclofenac. Antipyretic effects may be due to action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat dissipation.

#### Acute toxicity

LD50 and TDLo values for Diclofenac sodium are summarized in table 1.

#### Repeat-dose toxicity

Several repeated dose toxicity studies were reported in rats and dogs after oral administration of diclofenac sodium. The high dosed animals showed effects at gastro-intestinal, kidney and spleen sites.
<table>
<thead>
<tr>
<th>Carcinogenicity</th>
<th>Diclofenac is not listed as a carcinogen by IARC, NTP or OSHA.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“In vitro”/“in vivo” genotoxicity studies</strong></td>
<td>There were no positive results in either mutation or clastogenicity assays</td>
</tr>
<tr>
<td>Reproductive/developmental toxicity</td>
<td>Some effects related to a decrease of fetal weight were reported in reproductive and developmental toxicity studies in mice and rats. No malformations were observed in vivo studies, however teratogenic effects of diclofenac during organogenesis have been reported using a whole rat embryo culture model. Classified as Pregnancy category C by FDA and ADEC.</td>
</tr>
</tbody>
</table>

**IDENTIFICATION OF CRITICAL EFFECTS**

<table>
<thead>
<tr>
<th>Most sensitive indicator of an adverse effect seen in non-clinical toxicity data</th>
<th>After repeated dose toxicity studies in animals the more typical target organs were the gastro-intestinal tract and the kidney.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical therapeutic and adverse effects</td>
<td>Diclofenac is associated with risks of gastrointestinal (GI) and cardiovascular (CV) toxicities. The GI system is the major site of adverse effects.</td>
</tr>
</tbody>
</table>
NOAEL | 1 mg/kg/day. (Rats, 26 weeks). (FDA, NDA 22-122).

<table>
<thead>
<tr>
<th>APPLICATION OF ADJUSTMENT FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UFA: Extrapolation between species</strong></td>
</tr>
<tr>
<td><strong>UFH: Inter-individual variability</strong></td>
</tr>
<tr>
<td><strong>UFS: Toxicological study chronic or acute</strong></td>
</tr>
<tr>
<td><strong>UFL: NOAEL vs LOAEL</strong></td>
</tr>
<tr>
<td><strong>UFD: Database completeness</strong></td>
</tr>
</tbody>
</table>

| MODIFYING FACTOR (MF) | 2 | Because reproductive/developmental toxicity were controversial for the animal studies. |
| PK CORRECTION | 1 | Not necessary route-to-route extrapolation |

“Reproduction or unauthorized distribution is strictly prohibited. The present document is licensed to a “single client” or organization, and may not be re-sold, copied, or redistributed to other companies or organizations. The use by any company other than the one indicated in the watermark is prohibited. The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement.”

AZIERTA Contract Scientific support Consulting, S.L.
C/ Francisco González Leal 2  
28233 Pozuelo de Alarcón  
Madrid

PCB, C/Baldiri Reixac, 4, 4ª pl.  
Of. B-8, Ed. Torre I.  
08028 Barcelona

CM Los Ejecutivos  
Av. Pedro de Heredia Piso 3, Dphco 307  
Cartagena de Indias (Colombia)

R.M. de Madrid, Tomo 24.326, Folio 172, Sección 8, Hoja M-437435. CIF: B-85125334
4. IDENTIFY OF THE ACTIVE SUBSTANCE

Synonyms: diclofenac acid;

IUPAC name: 2-[2-(2,6-dichloroanilino) phenyl] acetic acid

Chemical Abstracts Service (CAS) Registry Number: 15307-86-5.

Molecular formula: C₁₄H₁₁Cl₂NO₂

Molecular weight: 296.15 g/mol

Figure 1. Structure of Diclofenac (ChemIDPlus)
It is primarily available as the sodium salt: **Diclofenac sodium**

**IUPAC name**: sodium;2-[2-(2,6-dichloroanilino) phenyl] acetat

**Chemical Abstracts Service (CAS) Registry Number**: 15307-79-6

**Molecular formula**: C\textsubscript{14}H\textsubscript{10}Cl\textsubscript{2}NNaO\textsubscript{2}

**Molecular weight**: 318.14 g/mol.

**Chemical Description and Physical Properties**: odorless, yellowish-white, crystalline powder sparingly soluble in water.

![Figure 2. Structure of Diclofenac sodium (ChemIDPlus)](image)

5. OBJECTIVE AND SEARCH STRATEGY

In accordance with the ISPE Risk-Mapp Baseline Guide (ISPE, 2010 and Walsh, A., 2011), with consideration to the methods discussed by Sargent, et al. (2013), the determination of health based exposure limits for a residual active substance is based on the calculation of the Acceptable Daily Exposure (ADE) values. The ADE represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime (ISPE, 2010).

Determination of a ADE 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 uncertainty or adjustment factors to account for various uncertainties and to extrapolate to the “true” no-effect level in the sub-population of interest.

Using the uncertainty/modifying factor method for determining acceptable daily exposure (ADE) values, as presented in the ISPE Risk-Mapp Baseline Guide (ISPE, 2010), an ADE can be calculated applying the following equation:

\[
\text{ADE (mg/day)} = \frac{\text{NOAEL or LOAEL (mg/kg/day)}}{\text{UFC} \times \text{MF} \times \text{PK}} \times \text{Body weight (kg)}
\]

where:
- ADE = Acceptable Daily Exposure (mg/day)
- NOAEL = No-Observed-Adverse-Effect Level (mg/kg/day)
- UFC = Composite Uncertainty Factor
- MF = Modifying Factor
- PK = Pharmacokinetic Adjustment(s)

The NOAEL value has been used to calculate a ADE in this study.

It is the purpose of this document to provide a brief summary of the scientific information relative to diclofenac compound. All the information presented in this document is fully based on published data.

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.

"Reproduction or unauthorized distribution is strictly prohibited. The present document is licensed to a “single client” or organization, and may not be re-sold, copied, or redistributed to other companies or organizations. The use by any company other than the one indicated in the watermark is prohibited. The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement"
Diclofenac is an acetic acid nonsteroidal antiinflammatory drug (NSAID) with analgesic and antipyretic properties. Diclofenac is used to treat pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis (PubChem).

ATC code for systemic use: M01AB05 (WHO, 2015).

6. INTRODUCTION

Diclofenac is an acetic acid nonsteroidal antiinflammatory drug (NSAID) with analgesic and antipyretic properties. Diclofenac is used to treat pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis (PubChem).

7. HAZARD IDENTIFICATION

In this section, an evaluation of all pertinent information relative to the substance’s potential to cause harm in humans is performed. This section includes an expert discussion with respect to the critical end-points, a rationale for the discussion of the choice of end points and dose. Pivotal animal and human studies were sources to the original references when possible. The study design, description of findings and accuracy of the report were revised.

a. Pharmacodynamics data

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models.

- Anti-inflammatory effect.

The principal therapeutic effects of NSAIDs derive from their ability to inhibit prostaglandin production. NSAIDs act by inhibiting the prostaglandin (PG) G/H synthase enzymes, known as the cyclooxygenases (COX) and consequently decrease the synthesis of prostaglandins. The inhibition of COX-2 (which is inducible by inflammatory stimuli) is thought to mediate, in large part, the antipyretic, analgesic, and anti-inflammatory actions of NSAIDs, while the inhibition of COX-1 and COX-2 accounts for

"Reproduction or unauthorized distribution is strictly prohibited. The present document is licensed to a “single client” or organization, and may not be re-sold, copied, or redistributed to other companies or organizations. The use by any company other than the one indicated in the watermark is prohibited. The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement”
unwanted adverse effects.Diclofenac inhibits both COX-1 and COX-2 but it has higher selectivity for COX-2. (Novartis,2014).

- Analgesic effect.

Diclofenac and other NSAIDs exert their analgesic effect not only through peripheral inhibition of prostaglandin synthesis but also through a variety of other peripheral and central mechanisms.

- Fever effects.

Fever may reflect infection or result from tissue damage, inflammation, etc. These conditions all enhance formation of cytokines that increase synthesis of PGE2 in circumventricular organs in and adjacent to the preoptic hypothalamic area; PGE2 increases cyclic AMP and triggers the hypothalamus to elevate body temperature by promoting an increase in heat generation and a decrease in heat loss. NSAIDs suppress this response by inhibiting PGE2 synthesis. As with pain, NSAIDs do not inhibit the fever caused by directly administered prostaglandins; rather they inhibit fever caused by agents that enhance the synthesis of cytokines, which presumably cause fever, at least in part, by inducing the endogenous synthesis of prostaglandins (Goodman and Gilman, 2006).

b. Acute toxicity

According to the information contained in the ChemIDplus database and RTECS (diclofenac sodium), LD50 values for rat and mouse administered intraperitoneal and orally are summarized in table 1. TDLo values for man/woman are also summarized.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Test Type</th>
<th>Route</th>
<th>Reported Dose (Normalized Dose)</th>
<th>Effect</th>
<th>Source</th>
</tr>
</thead>
</table>

"Reproduction or unauthorized distribution is strictly prohibited. The present document is licensed to a "single client" or organization, and may not be re-sold, copied, or redistributed to other companies or organizations. The use by any company other than the one indicated in the watermark is prohibited. The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement."
<table>
<thead>
<tr>
<th>Species</th>
<th>Toxicological Dose</th>
<th>Route</th>
<th>Toxicological Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman</td>
<td>30 mg/kg</td>
<td>Oral</td>
<td>Gastrointestinal nausea or vomiting</td>
<td>PGMJAO Postgraduate Medical Journal. (Blackwell Scientific Pub. Ltd., POB 88, Oxford, UK) V.1- 1925 69,486,1993</td>
</tr>
<tr>
<td>Woman</td>
<td>183 mg/kg</td>
<td>Oral</td>
<td>Liver - hepatitis, fibrous (cirrhosis, post-necrotic scarring)</td>
<td>BJCPAT British Journal of Clinical Practice. (Medical News Group, 1 Bedford St., London WC2E 9HD, UK) V.10(10)- 1956- 43,125,1989</td>
</tr>
<tr>
<td>Woman</td>
<td>270 mg/kg</td>
<td>Oral</td>
<td>Gastrointestinal ulceration or bleeding from large intestine</td>
<td>AIMDAP Archives of Internal Medicine. (AMA, 535 N. earborn St., Chicago, IL 60610) V.1- 1908- 152,625,1992</td>
</tr>
<tr>
<td>Mouse</td>
<td>170 mg/kg</td>
<td>Oral</td>
<td></td>
<td>Pharmazie. Vol. 37, Pg. 148, 1982.</td>
</tr>
</tbody>
</table>

"Reproduction or unauthorized distribution is strictly prohibited. The present document is licensed to a "single client" or organization, and may not be re-sold, copied, or redistributed to other companies or organizations. The use by any company other than the one indicated in the watermark is prohibited. The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement"
Single dose experiments for diclofenac sodium, summarized in Voltaren report (FDA, NDA 19-201), showed that the acute oral or intravenous LD50 in mice, rats and dogs is generally between 90-250 mg/kg. Rabbits appear more sensitive with an iv LD50 around 60 mg/kg and monkeys considerably less sensitive with an oral LD50 around 3200mg/kg.

c. Repeat dose toxicity

In a repeated dose toxicity study, diclofenac sodium was administered orally at 0.3 or 1 mg/kg bw/day to dogs for four weeks. At the lowest dose cortical tubular dilatation was observed in the kidneys of most animals. In addition, females showed urothelial hyperplasia in the renal papillae. The high dosed animals showed severe effects at gastro-intestinal, kidney and spleen sites accompanied by diarrhea, anemia, protein loss and kidney dysfunction. Chronic inflammation of the livers of treated males and females was seen, in females associated with bile duct proliferation (EMEA, 2003).

Several repeated dose toxicity studies were reported in rats after oral administration of diclofenac sodium. Oral administration of 0.5, 2.5 and 5.0 mg/kg body weight doses for 91 days, resulted in significant decrease of absolute and relative liver and epididymis weight in males treated with 5.0 mg/kg body weight. No adverse and toxic effects were observed at 0.5 and 2.5 mg/kg body weight. A NOEL was determined as 2.5 mg/kg bw. (EMEA, 2003). In a second rat study oral doses up to 16 mg/kg bw /day were tested during 31 days (FDA, NDA 22-122). In this case hypertrophy of mesenteric lymph nodes was reported with doses from 4-16 mg/kg. Intestinal mucosal hemorrhages, weight loss, reduced food intake hypertrophy of spleen, peritonitis and gastrointestinal ulceration were also reported at higher doses. NOAEL value was established at 2 mg/kg bw/day. The same NOAEL value was reported in a rat study with oral doses up to 6 mg/kg/day during 13 weeks. A fourth repeated dose toxicity study in rats tested oral doses of 0,25-0,5- 1- 2 and 4 mg/kg bw/day during 26 weeks. The authors reported hypertrophy of mesenteric lymph nodes with doses of 2-4 mg/kg and necrosis of cecal mucosa in the
animals treated with the higher dose. The NOAEL value for diclofenac oral administration in rats established in this study was 1 mg/kg bw/day (FDA, NDA 22-122).

Diclofenac sodium was administered intramuscularly to Beagle dogs daily at doses of 0, 0.1, 0.5 and 1.0 mg/kg bw for 90 days in a study of repeat dose toxicity (EMEA, 2003). Dose of 1.0 mg/kg bw showed a lower body weight gain, reduced food consumption, enhanced incidence of scours, often with blood admixture, reduction of hemoglobin, and hematocrit values and red blood cell counts in males and females, increases in white blood cells and a significant elevation of platelet and segmented neutrophil in males and in both sexes a reduction of serum albumin and total protein content. Aspartate aminotransferase activity was also enhanced and the excretory function of the kidneys was reduced transiently. Microscopic examination showed atrophy of the epithelium in the small intestine villi, focal enteritis, focal erosions, desquamation and hyperemia in animals at 1.0 mg/kg bw, and sporadically, with a lower intensity in the group treated with 0.5 mg diclofenac/kg bw. A parenteral NOEL was set at 0.1 mg/kg bw.

d. Carcinogenicity

No oncogenic potential was demonstrated with diclofenac sodium in a 2 year carcinogenicity study in male mice given up to 0.3 mg/kg of body weight /day or in female mice given up to 1 mg/kg /day (Thomson Micromedex, 2004)

Diclofenac is not listed as a carcinogen by IARC (International Agency for Research on Cancer), NTP (National Toxicology Program) or OSHA (Occupational Safety and Health administration).

e. In vitro / in vivo genotoxicity studies

The potential genetic toxicology of diclofenac sodium has been studied in a numerous in vitro and in vivo studies (NDA 19-201). There were no positive results in either mutation or clastogenicity assays. In vitro mutagenicity studies on diclofenac included reverse mutation in the Salmonella typhimurium assay and a chromosome aberration assay with human lymphocytes, both performed with and without metabolic activation. In vivo, the micronucleus assay in mouse bone marrow was also negative. It can be concluded that diclofenac is not mutagenic.
f. Reproductive and developmental toxicity

Several studies of reproductive and developmental toxicity in mice after oral administration of diclofenac, resulted in no significant related effects at dosages of 2-4 mg/kg/day. Toxic changes as reducing implantations, reduced fetal weight and reduced fetal ossification were reported in mice treated at 10-20 mg/kg/day from day 0 to 17 of gestation. No malformations were observed (FDA, NDA 22-122).

A one generation reproductive toxicity study in rats established adverse effects after repeated oral administration of diclofenac sodium at 0.5, 2.5 and 5.0 mg/kg bw. In females receiving diclofenac sodium at 2.5 and 5.0 mg/kg bw/day adverse effects on body weight, food consumption, mortality, percentage fertility, percentage of mated parental females, litter size and number, live birth index, adverse effects in the absolute and relative weights in liver, spleen and uterus, number of corpora lutea, pathological and histopathological effects were observed. NOEL value could not be established as a depression of parental body weight and a reduction in the percentage of mated females was still observed at 0.5 mg/kg bw.

In a two generation reproductive toxicity study, rats were administered diclofenac sodium orally at 0.25, 1.25 and 2.5 mg/kg bw/day. Adverse and toxic effects were reported at 2.5 mg/kg bw/day for food consumption, percentage of mated parental F1 females, litter size in F1 and F2 generations, sex distribution and a reduction of epididymides weight in parental F1 males. Mild adverse and toxic effects, manifest as a reduction in litter size in the F1 generation pups, and in the relative weights of epididymides in parental males at 1.25 and 2.5 mg/kg bw were observed. (EMEA, 2003) In this study NOEL values were determined as 1.25 mg/kg bw for fertility and 0.25 mg/kg bw for parental and neonatal toxicity.

Oral dose of 4 mg/kg bw/day of diclofenac was used in several studies of reproductive and developmental toxicity in rats. Decreased fetal weights and rib defects were some of the effects reported at this dose. Higher doses (10 mg/kg) also increased rate of resorption and increased fetal mortality (FDA, NDA 22-122).

The results of the in vivo reproductive and developmental toxicity studies (in mice, rats, rabbits, dog or monkeys) did not indicate a teratogenic potential of diclofenac. However teratogenic effects of diclofenac during organogenesis have been reported using a whole
rat embryo culture model (Chan et al., 2001). Rat embryos were exposed to various concentrations of diclofenac and scored for growth and differentiation at the end of the culture period. Total developmental score and score for caudal neural tube, flexion and hindlimb were significantly lower in embryos exposed to high concentrations of diclofenac (7.5 and 15.0 µg/ml), but no difference in these parameters was observed when embryos were exposed to low concentration of diclofenac (1.5, 2.5 and 5.0 µg/ml). This study concluded that diclofenac exerts direct teratogenic effects on rat embryos. The abnormalities were not specifically described.

There are no adequate and well controlled studies of diclofenac or other NSAIDs in pregnant women. Administration of NSAIDs during the latter part of pregnancy may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labor and delivery. The use of diclofenac during pregnancy should be avoided.

8. IDENTIFICATION OF CRITICAL EFFECTS

The steps deliberated to identify the nature of the adverse effect include its severity and persistence. If the substance causes multiple types of adverse effects, the critical effect is one that meets the severity and persistence criteria at the lowest intake.

a. Most sensitive indicator of an adverse effect seen in non-clinical toxicity data

After repeated dose toxicity studies in animals the more typical target organs were the gastro-intestinal tract and the kidney.

b. Clinical therapeutic and adverse effects

The main risks associated to diclofenac in clinical therapeutics are the following:

Cardiovascular Effects

- Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years
duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk.

- **Hypertension**

NSAIDs can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events.

- **Congestive Heart Failure and Edema**

Fluid retention and edema have been observed in some patients taking NSAIDs

**Gastrointestinal (GI) Effects**

- **Risk of GI Ulceration, Bleeding, and Perforation**

Diclofenac as other NSAIDs, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year.

**Renal effects**

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

**Hepatic Effects**

Elevations of one or more liver tests (transaminases) may occur during therapy with diclofenac sodium. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

**Hematological Effects**

Anemia is sometimes seen in patients receiving NSAIDs, including diclofenac. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Their effect on platelet function is quantitatively less, of shorter duration, and reversible.
Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to diclofenac.

9. RATIONAL FOR NOAEL VALUES SELECTION

For several decades, diclofenac has been one of the most widely used drugs in the world for the treatment of various inflammatory, chronic, and acute pain conditions and this extensive post-approval experience supports its safe and effective clinical use. Its pharmacological activity is also well established for the publications and also by its continuous clinical use. Several publications of diclofenac with data on original values of NOAEL could be identified.

Based on the description of the repeated dose toxicity studies, a NOAEL of 1 mg/kg/day was chosen as the most conservative approach. The toxicity study in rats reported adverse GI effects after repeated oral administration of diclofenac. The tested doses were 0.25, 0.5, 1, 2 and 4 mg/kg bw/day for 26 weeks (FDA, NDA 22-122).

10. APPLICATION OF ADJUSTMENT FACTORS (rational for the adjustment factors)

A series of modifying, or safety factors, are used when the NOAEL is based on studies of differing types and durations in differing species to provide a risk assessment for human exposure. Naumann and Weideman (1995) summarized the scientific basis for the uncertainty factors discussed below.

According to the ISPE Risk-Mapp Baseline Guide (ISPE, 2010) the Composite Uncertainty Factor (UCF) includes the following safety factors:

- Inter-species Differences (UF_A)
- Intra-species Differences (interindividual variability) (UF_H)
- Subchronic-to-Chronic Extrapolation (UF_S)
- LOAEL-to-NOAEL Extrapolation (UF_L)
- Database Completeness (UF_D)
These factors are similar to safety factors for PDE calculation (European Medicines Agency EMA (2014). “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)), and they are generally established according to Appendices 3 of the ICH Q3C (R4) and VICH GL 18.

a. UF_A: Interspecies differences

This uncertainty factor is used to extrapolate a NOAEL (or LOAEL) from animal studies to a human sub-population.

This factor takes into account the comparative surface area: body weight ratios for the species concerned and for man. Surface area (S) was calculated as: \( S = k M^{0.67} \) where M is the body mass and the constant, k, has been taken to be 10 according to the appendices 3 of the ICH guideline. For a 50 kg person the equation gives a surface area of 64.3 dm\(^2\); the surface area: body weight ratio is thus 2.76.

Applying the same calculation to other species and expressing the results as multiples of the human surface area: body weight ratio gives factors for the mouse = 12; for the rat = 5; for the monkey = 3; for the rabbit = 2.5; for the dog = 2. For other species, where the data are not so well established this factor is taken as 10.

As rat specie was used, value of 5 was assigned to UF_A.

b. UF_H: Inter-individual variability

This uncertainty factor reflects the variability that exists in the subpopulation of interest (i.e., the most susceptible subgroup) compared to the study population from which the NOAEL was derived in terms of systemic exposure for a given dose (kinetics) and differences in how the body responds (dynamics).

A factor of 10 is conventionally used to allow for differences between individuals in the human population, when animal studies are used as point of departure for ADE calculation.

c. UF_S: Subchronic-to-Chronic Extrapolation (Duration of exposure)

When the duration of the study used to identify the critical effect is different from the actual exposure scenario, an additional adjustment needs to be made.
A variable factor up to 10 takes into account the differing durations of exposure in the reported studies (ICH Q3C (R4)). For reproductive studies, a factor of 1 is used if the whole period of organogenesis is covered. A factor of 2 has been used for a 6-month study in rodents, or a 3.5-year study in non-rodents. A factor of 5 has been used for a 3-month study in rodents or a 2-year study in non-rodents and a factor of 10 for studies of a shorter duration. In all cases, the higher factor has been used for study durations between the time points e.g. a factor of 2 for a 9-month rodent study.

In this case a factor of 2 was established given that NOAEL was determined in rats in a 26-weeks study.

**d. UF_L: LOAEL-to-NOAEL Extrapolation**

A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

As the NOAEL was extracted, a factor of 1 was used in this study.

**e. UF_D: Database Completeness**

An additional uncertainty factor may be required if the overall toxicity database is incomplete. UF_D value for diclofenac was 1, as its toxicity is well established for the publications.

**11. MODIFYING FACTOR (MF)**

A modifying factor may also be considered if there is a need to address residual uncertainties not covered by the other factors (ISPE, 2010).

The nature of toxicity was considered as modifying factor (MF). A variable factor is applied when the toxicity produced is irreversible in nature i.e. carcinogenicity, neurotoxicity or teratogenicity (ICH Q3C (R4)). A factor of 10 is used when oncogenic or neurotoxic responses are present. A variable factor is used for reproductive toxicity effects as follows: 1 for embryo or fetal toxicity or mortality associated with maternal toxicity; 5 for embryo or fetal toxicity or mortality without maternal toxicity; 5 for a teratogenic effect with maternal toxicity and 10 for a teratogenic effect in the absence of
accompanying maternal toxicity.

A factor of 2 was established as MF. Although no carcinogenicity, neurotoxicity or mutagenicity was described, the data was contradictory in terms of developmental toxicity (teratogenic effects were reported with rat embryo culture models).

12. PK CORRECTION

In certain cases, route-to-route extrapolation may be appropriate when attempting to derive an ADE from a study conducted by a route that is different from the potential route of exposure (ISPE, 2010).

A PK factor of 1 was used in this case as NOAEL was extracted after repeated oral administration of diclofenac.

13. ADE CALCULATION

The ADE calculation is generally presented in the format:

\[
ADE \ (\text{mg/day}) = \frac{\text{NOAEL or LOAEL (mg/kg/day) } \times \text{ Body weight (kg)}}{\text{UFC (UFA x UFH x UFS x UFL x UFD) } \times \text{ MF } \times \text{ PK}}
\]

where:

\[\text{ADE = Acceptable Daily Exposure (mg/day)}\]
\[\text{NOAEL = No-Observed-Adverse-Effect Level (mg/kg/day)}\]
\[\text{UFC = Composite Uncertainty Factor}\]

where:

- \(\text{UFA}\) Inter-species Differences
- \(\text{UFH}\) Intra-species Differences (interindividual variability)
- \(\text{UFS}\) Subchronic-to-Chronic Extrapolation
- \(\text{UFL}\) LOAEL-to-NOAEL Extrapolation
- \(\text{UF}_{\text{D}}\) Database Completeness

"Reproduction or unauthorized distribution is strictly prohibited. The present document is licensed to a “single client” or organization, and may not be re-sold, copied, or redistributed to other companies or organizations. The use by any company other than the one indicated in the watermark is prohibited. The Parties agree that, in the event of violation of this clause, without limiting the Disclosing Party’s other rights and remedies, the Disclosing Party shall be entitled to an injunction and other equitable relief, including but not limited to specific performance, against the Receiving Party for breaching or threatening to breach this Agreement”
MF = Modifying Factor
PK = Pharmacokinetic Adjustment(s)

\[
ADE (\text{mg/day}) = \frac{1 \text{ (mg/kg/day)} \times 50 \text{ (kg)}}{(5 \times 10 \times 2 \times 1 \times 1) \times 2 \times 1} = 0.25 \text{ mg/day}
\]
12. REFERENCES

1. Appendix 3 of ICH Q3C (R4) "Impurities: Guideline for Residual Solvents"
2. Appendix 3 of VICH GL 18 on "Residual solvents in new veterinary medicinal products, active substances and excipients (Revision)"
10. FDA, NDA 19-201. Voltaren tablets, Diclofenac sodium


17. RTECS. Diclofenac sodium. Number AG6330000. Registry of Toxic Effects of Chemical Substances.


ANNEX 1: PHARMACOKINETICS AND METABOLISM

The pharmacokinetics characteristics according to the most recent label for Voltaren and Voltaren-XR (2009) are the following:

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1 to 4.5 hours and a reduction in peak plasma levels of <20%.

Distribution

The apparent volume of distribution (V/F) of diclofenac sodium is 1.4 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 μg/mL) achieved with recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4’-hydroxy-, 5-hydroxy-, 3’-hydroxy-, 4’,5-dihydroxy- and 3’-hydroxy-4’-methoxy diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4’-hydroxy- and 5-hydroxydiclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects. However, diclofenac metabolites undergo further glucuronidation and sulfation followed by biliary excretion.

One diclofenac metabolite 4’-hydroxy- diclofenac has very weak pharmacologic activity.
Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours.
ANNEX 2. SUMMARY OF THE EXPERT CV