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ANNEX 2: SUMMARY OF THE EXPERT CV 24

1. BASIC INFORMATION

Company name:	
Company Address:	
Expert name:	
Signature:	
Date:	
Assessment review data:	
Chemical name:	Piroxicam
Drug Product:	piroxicam 20 mg capsules

2. HAZARDS IDENTIFIED

	Yes	No	Unknown
Genotoxicant	☐	☒	☐
Reproductive developmental toxicant	☐	☐	☒
Carcinogen	☐	☒	☐

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

PDE Value:	$PDE = \frac{NOAELxWeight\ adj}{F1xF2xF3xF4xF5} = \frac{1\,mg/kgx50kg}{5x10x1x5x1} = 0,2mg/day$

HAZARD IDENTIFICATION:	
Non-clinical pharmacodynamics data:	NSAIDS, non-selective COX inhibitor. Possesses analgesic, antipyretic, and anti-inflammatory properties and inhibits platelet aggregation in animal models.
Repeat-dose toxicity:	After repeat- dose studies in rat (3 and 18 months) and monkey (3 months), the main target organs were the gastro-intestinal system and additionally the kidney in the 18 months study in rats.
Carcinogenicity:	No evidence of carcinogenic potential was seen in rats at doses up to 1 mg/kg/day for 2 years. Piroxicam is not listed as a carcinogen by IARC, NTP or OSHA.
"In vitro"/"in vivo" genotoxicity studies:	Piroxicam was negative in the Ames model for bacterial mutagenicity with Salmonella E. coli and also a negative results was obtained in human lymphocytes cells (in vitro cytogenetics).
Reproductive/ developmental toxicity:	Piroxicam is not teratogenic. Some effects related to a slight inhibition of postnatal body weight gain was seen in peri- and postnatal development studies in rats (NOAEL 2 mg/kg/day) although the confirmation in human is controversial. Classified as Pregnancy category C by FDA and ADEC.

IDENTIFICATION OF CRITICAL EFFECTS:	
Most sensitive indicator of an adverse effect seen in non-clinical toxicity data:	Gastro-intestinal and kidney effect.
Clinical therapeutic and adverse effects:	Beneficial therapeutics effects: pain, inflammation, fever. Side effects link to target: stomach mucosa and platelet stickiness. The gastrointestinal system is the major site of adverse effects. Others adverse effects are cardiovascular risk, dizziness, headaches, skin rashes, respiratory depression or hepatitis.

NOAEL:	**1mg/kg/day rat 18 months study (MSDS, Pfizer, 2007)**

APPLICATION OF ADJUSTMENT FACTORS		
F1: Extrapolation between species (2-12)	5	Based on surface area calculations for rat.
F2:Inter-individual variability (10)	10	Conventionally used to allow for differences between individuals in the human population.
F3: Toxicological study Chronic or acute (10 is study duration < 4 weeks) (1-10). Not included genotoxicity, carcinogenicity, neurotoxicity and teratogenicity	1	Based on length of the study equivalent to at least one half-life (1 year for rodent). Study of 18 months duration in rats.

F4: for severe toxicity	5	Because reproductive toxicity are controversial for the animal studies.
F5: NOAEL vs LOAEL (10 if LOAEL)	1	Because NOAEL value was used for PDE calculation.

PK CORRECTION:	Not applied.

4. IDENTITY OF THE ACTIVE SUBSTANCE

Synonyms: 4-Hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazin-3-caboxyamid-1,1-dioxid [German]; 4-Hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide; 4-Hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide; BAXO; CHF 1251; CP 16171; CP-16,171; Feldene; Piroftal; Piroxicamum [INN-Latin]; Pyroxycam; Roxicam; 2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide; [ChemIDplus]
Chemical Abstracts Service (CAS) Registry Number: 36-322-90-4
Chemical Description and Physical Properties: white crystalline solid (Merck index)
Molecular formula: C15H13N3O4S
Molecular weight: 331.348
Melting point: 198-200°C (ChemIDPlus)

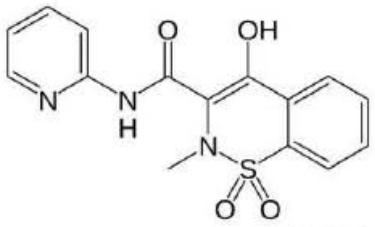

Figure 1. Structure of Piroxicam.

5. OBJECTIVE AND SEARCH STRATEGY

In accordance with Technical Report No. 29 (Revised 2012) 'Points to Consider for Cleaning Validation' (PDA), a calculation of Acceptable Residue Level should be provided based on two main parameters: a relevant toxicity data (No Observable Adverse Effect Level (NOAEL) or Lethal Dose (LD_{50})); and Acceptable Daily Intake (ADI). The 'No observed adverse effect level' (NOAEL), was obtained and used to calculate a PDE (see below).

It is the purpose of this document to provide a brief summary of the scientific information relative to Piroxicam compound. All the information presented for 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, Toxline, Medline, NTP (National Toxicology program), GESTIS (German database on hazardous substances), 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 Dank) and data from medical agencies such as AEMPS (Agencia Española de Medicamentos y Productos Sanitarios), CIMA (Centro de Información on-line de medicamentos), EMA (European Medicinal Agency), FDA (Food and Drug Administration) and ECHA (European Chemical Agency). The initial searched term was "piroxicam". Additional databases like RTECS (Registry of Toxic Effects of Chemical Substances), USP (US Pharmacopeial convention), JECFA (Joint FAO/WHO expert committee on Food additives), several MSDS (Material Safety Datasheet), IRIS (Integrated Risk Information System), CCRIS (Chemical carcinogenesis research Information system), GeneTox, MICROMEDEX, EFSA (European Food Safety Authority), International Programme on medical safety (INCHEM), CICAP (Concise International Chemical Assessment Documents), were also incorporated during the searching process. In addition, the reference book Goodman and Gilman (2006) was also consulted.

6. INTRODUCTION

Piroxicam is a non-steroidal anti-inflammatory agent with analgesic and antipyretic activity. Its ATC code M01AC01 (Oxicans, non-steroids anti-inflammatory and anti-rheumatic product). Piroxicam is indicated for the symptomatic relief of rheumatoid arthritis, osteoarthritis or ankylosing spondylitis. The maximum recommended dose is 20 mg. The main advantage of Piroxicam is its long half-life, which permits once-a-day dosing (Goodman and Gilman, 2006).

7. HAZARD IDENTIFICATION

In this section and evaluation of all pertinent information relative to the substance's potential to cause harm in humans is performed. This section include 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 sourced to the original references when possible. The study design, description of findings and accuracy of the report were revised.

a. Pharmacodynamics data

Piroxicam is a well-established product, with a well-known mechanism of action.

The principal therapeutic effects of NSAIDs derive from their ability to inhibit prostaglandins production. The first enzyme in the prostaglandin synthetic pathway is prostaglandin G/H synthase, also known as cyclooxygenase (COX) (See Figure 2 A).

Anti-inflammatory effect: This enzyme converts arachidonic acid (AA) to the unstable intermediate PGG2 and PGH2 and leads to the production of thromboxane A2 (TXA2) and a variety of prostaglandins (Goodman and Gilman, 2006). Therapeutics doses of piroxicam reduces prostaglandin biosynthesis in human, mediating their inflammatory activity. The inhibition of the different prostaglandins in turn mediate a variety of physiological effects both beneficial and pathological, as seen in figure 2 B (Vane and Botting, 2003). Piroxicam is an enolic acid (oxicam) that inhibit in a non-selective way COX-1 and COX-2. COX-I, expressed constitutively in many tissues, and COX-2 (discovered in 1990), an induced isoform having elevated expression in inflamed tissues. COX-1 is thought to be involved in ongoing "housekeeping" functions, for example, gastric cytoprotection, while COX-2 is the isoform implicated in the pathological effects mentioned above (Xie et al, 1993).

A) B)

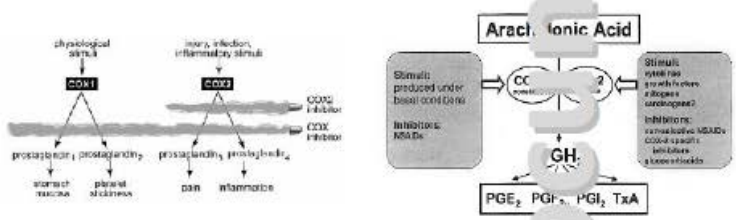

Figure 2. A) Generation of prostanoids by COX-1 and COX-2 enzymes: stimuli and inhibitors. PG = prostaglandin; TxA = thromboxane A (Husain et al., 2002). B) Schematic representation of the physiological and pathological action of COX-1 and COX-2 enzymes, which are blocked by piroxicam.

Analgesic effect: Although NSAIDs are usually classified as mild analgesics, they are particularly effective when inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli. NSAIDs do not affect hiperalgesia or pain caused by the direct action of prostaglandins; their actions are due to inhibition of prostaglandin synthesis.

Fever effects: Regulation of body temperature requires a delicate balance between the production and loss of heat and the hypothalamus regulates the set point at which body temperature is maintained. NSAIDs promote the return of temperature to this set point by inhibition of PGE2. NSAIDs inhibit the fever caused by agents that enhance the synthesis of IL-1 and other cytokines which in turns cause fever at least in part through inducing the endogenous synthesis of prostaglandins (Goodman and Gilman, 2006).

b. Acute toxicity

According to the information contained in the safety data sheet of Feldene (MSDS, Feldene, Pfizer 2007) and the ChemIDPlus database, The **LD_{50}** values for rats, mice and dog administered intraperitoneal or orally are summarized in Table 1.

Table 1. Values of L LD_{50} for mouse, rat, hamster, guinea pig, dog and monkey after oral, subcutaneous, rectal and skin intra-peritoneal administration.

Specie	Administration route	LD_{50} (mg/kg)	Target organ	Reference
Mouse	oral	360	Not reported	(MSDS, Feldene, Pfizer 2007)
	ip	290	Not reported	
	ip	360	Not reported	(MSDS, Feldene, Pfizer 2007)
	oral	250	Not reported	
	sc	300	Behavioral: somnolence (general depression activity) Lungs, thorax or respitatory: respiratory depression. Behavioral: Changes in motor activity (specific assay)	ChemIDPlus

Table 1. Values of L LD_{50} for mouse, rat, hamster, guinea pig, dog and monkey after oral, subcutaneous, rectal and skin intra-peritoneal administration (cont.).

Specie	Administration route	LD_{50} (mg/kg)	Target organ	Reference
Rat	oral	270	Not reported	(MSDS, Feldene, Pfizer 2007)
	oral	216	Not reported	ChemIDPlus
	ip	335	Behavioral: somnolence (general depression activity) Lungs, thorax or respitatory: respiratory depression. Behavioral: Changes in motor activity.	ChemIDPlus
	ip	220	Not reported	(MSDS, Feldene, Pfizer 2007)
	rectal	400	Behavioral: analgesia	ChemIDPlus
	skin	>5000	Not reported	ChemIDPlus
	sc	148	Behavioral: somnolence (general depression activity) Lungs, thorax or respitatory: respiratory depression. Behavioral: Changes in motor activity.	ChemIDPlus

Table 1. Values of L LD_{50} for mouse, rat, hamster, guinea pig, dog and monkey after oral, subcutaneous, rectal and skin intra-peritoneal administration (cont.).

Specie	Administration route	LD_{50} (mg/kg)	Target organ	Reference
Guinea pig	oral	388	Not reported	ChemIDPlus
Hamster	oral	170	Not reported	ChemIDPlus
Dog	oral	>700	Not reported	(MSDS, Feldene, Pfizer 2007)
	oral	108	Behavioral: somnolence (general depression activity) Lungs, thorax or respitatory: respiratory depression. Behavioral: Changes in motor activity	ChemIDPlus
Monkey		1000	Not reported	(MSDS, Feldene, Pfizer 2007)

c. Repeat dose toxicity

In additional reported studies compiled in the MSDS (MSDS, Pfizer, 2007), the **NOAEL** values after multiple dose administration are summarized in Table 2.

Subchronic oral toxicity studies were conducted in rats at doses up to 25 mg/kg/day and monkeys at doses up to 10 mg/kg/day for 3 months. In rats, gastric ulcers were seen at 10 and 25 mg/kg/day in males and females (more severe and numerous). NOAEL was established at 5 mg/kg/day (see Table 2). In monkeys, minimal gastrointestinal lesions were observed at 10 mg/kg/day. In another study of 14 and 28 days duration in rats at the dose of 5 mg/kg/day piroxicam caused multiple gastric erosions and hemorrhage in rats after 14 and 28 days of administration. The levels of

myeloperoxidase activity (as an index of neutrophil infiltration) were not changed compared with control after drug treatment. All the hematological parameters obtained after drugs administration for 14 and 28 days were in the range of normal values, and a significant increase in platelet levels could be observed in the group treated with 5 mg/kg of piroxicam for 14 days. Aspartate aminotransferase (AST or GOT) increased significantly after 14 days, but after 28 days the values returned to normality. Creatinine and urea did not undergo significant changes except for the piroxicam 14-day 5 mg/kg group, in which uremia increased significantly over normal values (Villegas, 2002).

Chronic toxicity of piroxicam was evaluated for 18 months in mice at doses up to 8 mg/kg/day and rats at doses up to 3 mg/kg/day, and for 1 year in dogs at a dose of 1mg/kg/day and monkeys at doses up to 10 mg/kg/day. Gastrointestinal lesions and kidney necrosis were observed in mice at 4 or 8 mg/kg/day and male and female rats at 3 mg/kg/day and one female at the low dose (0.3 mg/kg). In dogs, gastrointestinal and kidney toxicity was associated with treatment. In monkeys, kidney toxicity was seen in the high dose females; no evidence of gastro-intestinal toxicity was seen at the dosage levels tested.

Table 2. Values of NOAEL for rat and monkey after oral administration for 3 and 18 months.

Duration (months)	Specie	Route	Dose (mg/kg/day)	End point	Target organ
3	Rat	Oral	5	NOAEL	Gastro-intestinal system
3	Monkey	Oral	2.5		Gastro-intestinal system
18	Rat	Oral	1	NOAEL	Gastro-intestinal system, Kidney

d. Carcinogenicity

According to the **carcinogenic** potency database (CPDB), assays in male rats showed no positive evidence in carcinogenic potential for piroxicam. No evidence of carcinogenic potential was seen in rats at doses up to 1 mg/kg/day for 2 years. Piroxicam 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

In vitro **Genotoxicity studies** (MSDS, IARC, International Agency for Research on Cancer 1987) revealed that piroxicam was negative in the Ames model for bacterial mutagenicity with Salmonella typhimurium, E. coli and also a negative results was obtained in human lymphocytes cells (in vitro cytogenetics).

The mutagenic potential of piroxicam has been evaluated using in vivo micronucleus test. Four dose levels for each compound were used and bone marrow cells were examined 24 hours after the administration. The results show that doses applied do not induce a statistical significant increase of the frequency of micronucleated polychromatic erythrocytes (Gris et al., 2008).

f. Reproductive and developmental toxicity

With regard to **developmental toxicity**, no effects on fertility or reproductive performance were observed in rats (see Table 3). In mice after intraperitoneal administration of piroxicam (0.28, 0.56 or 0.84 mg/kg) for a chronic administration during 60 (males) or 35 (females) days, Piroxicam at the lowest dose diminished the concentration of spermatozoa found in the uterus after mating. No other effects were observed (parameters evaluated were: a) in females, spontaneous and induced ovulation, oocyte maturity and spermatozoa migration through genital tract, b) in males, epididymal spermatozoa concentration, motility, viability, resistance to hypoosmotic shock, acrosomal status and membrane maturity and c) in both genders, in vitro and in vivo fertilization, reproductive hormones plasma levels and cyclooxigenase inhibition in reproductive tissues) (Martini, 2008).

According to both the FDA pregnancy category and the Australian Drug Evaluation Committee's (ADEC), piroxicam is classified as category C (either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available). Given the controversial data drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Both the American Academy of Pediatrics and the Micromedex rate a minimal risk to the infant when piroxicam is used during breastfeeding. The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the infant when used during breastfeeding. Although piroxicam appears in breast milk, the concentration is too low to be pharmacologically significant. Only small amounts of

piroxicam were observed in breast milk during long-term therapy in lactating women (DrugDex). Four women with arthritis were treated with oral piroxicam 20 mg once daily for up to 52 days. The mean milk concentrations at steady-state were 78 µg/L (maximum 141 µg/L); the concentrations in breast milk represented 1% to 3% of simultaneous maternal plasma levels. Accumulation of the drug was not observed in breast milk relative to plasma. All infants remained healthy during the study period. In one breastfed infant, piroxicam or its metabolites were not detected in urine samples. The estimated daily dose of piroxicam ingested by the breastfeeding infant averaged 3.5% (maximum, 6.3%) of the maternal dose. This report suggests that piroxicam is relatively safe when given chronically to a breastfeeding mother.

Table 3. Values of NOAEL for rat and rabbit after studies of developmental toxicity after oral administration.

Study type	Specie	Route	Dose (mg/kg/day)	End point	Effects
Reproductive and fertility	Rat	Oral	10	NOAEL	No effect at maximum dose
Peri-postnatal development	Rat	Oral	2	LOAEL	Developmental toxicity
Fertility and Embryonic Development	Rat	Oral	10	NOAEL	No effects at maximum dose, Not Teratogenic
Fertility and Embryonic Development	Rabbit	Oral	10	NOAEL	No effects at maximum dose, Not Teratogenic

8. IDENTIFICATION OF CRITICAL EFFECTS

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 or the kidney.

b. Clinical therapeutic and adverse effects

By oral route, the main risk associated with piroxicam in clinical therapeutics are the following:

Cardiovascular Risk: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Piroxicam is contraindicated for the treatment of perioperative pain in the setting of CABG surgery (DrugDex).

Gastrointestinal Risk: NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (DrugDex).

Asthma, urticaria, or allergic-type reaction: Following administration of aspirin or other NSAIDs; severe anaphylactic-like reactions have been reported, including rare fatalities (DrugDex).

9. RATIONAL FOR NOAEL VALUE SELECTION

Piroxicam is well established anti-inflammatory agent.

As for all NSAIDs, piroxicam should always be used at the lowest dose for the shortest possible duration to control symptoms. The European Medicines Agency (EMEA) has recently completed a review of the safety of the non-steroidal anti-inflammatory drug (NSAID) piroxicam. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that piroxicam's benefits still outweigh its risks, but, based on safety grounds, only in certain, limited indications. In addition, the CHMP concluded that piroxicam-containing medicines should no longer be used for the treatment of acute (short-term) pain and inflammation.

Toxicological data reveal no special hazard for humans, based on published data. Its pharmacological activity is also well established, not only for the numerous publications, but also by its continuous clinical use. But in spite of this experience, few publications of piroxicam with data on original values of NOAEL could be identified.

Based on the description of the repeated dose studies and the developmental toxicity studies, a NOAEL of 1 mg/kg/day was chosen as the most conservative approach. This NOAEL was obtained after studies of Piroxicam in rats for 18 months. The target organ

for this studies were the gastrointestinal system and the kidney. After long-term treatment morphologic lesions of the kidney and increase in voided urine volume, sodium and potassium were observed. Injuries of the tubules and changes in kidney function were more pronounced in female rats (Murn, 1989).

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. These factors were generally established according to Appendices 3 of the ICH Q3C (R4) and VICH GL 18 and the values of Connelli (Connelli, 1997).

a. F1: Interspecies differences

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: $S = kM^{0.67}$ where M is the body mass and the constant, k, has been taken to be 10 according to the
appendices 3 of te 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 rabbit = 2.5; for the dog = 2. For other species, where the data are not so well established the factor F1 is taken as 10.

Therefore a factor of 5 (for the rat) was used in the calculations.

b. F2: Intra-individual differences

A factor of 10 is conventionally used to allow for differences between individuals in the human population.

c. F3: Duration of exposure

A variable factor up to 10 takes into account the differing durations of exposure in the reported studies. A factor of 1 has been used for studies that last at least one half lifetime (1 year for rodents or rabbits, 7 years for non-rodents cats, dogs and monkeys). 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 1 was establish given that the lower NOAEL was determine in rats in a study of 18 moth duration.

d. F4: Nature of toxicity

A variable factor applied when the toxicity produced is irreversible in nature i.e oncogenicity, neurotoxicity or teratogenicity. A factor of 10 has been used when oncogenic or neurotoxic responses are present. A variable factor has been used for reproductive toxicity effects as follows: 1 for embryo or foetal toxicity or mortality associated with maternal toxicity. 5 for embryo or foetal toxicity or mortality without accompanying maternal toxicity. 5 for a teratogenic effect accompanied by maternal toxicity. 10 for a teratogenic effect in the absence of accompanying maternal toxicity.

A factor of 5 was established. Although no oncogenicity or neurotoxicity or teratogenicity was described, the data was contradictory in terms of toxicity to the foetus.

e. F5: Quality of data

A variable factor, up to 10, applied to results in which a NOAEL has not been established, the PDE being derived from a LOEL. The size of the factor depends on the judgment of the toxicologist taking into account the severity of the toxicity seen and any dose-response information that may be present.

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

The PDE calculation shown in this document have been presented in the format:

$$PDE\left(\frac{mg}{day}\right) = \frac{NOAEL\ or\ LOAEL\left(\frac{mg}{kg}\right) x\ Weight\ adjustmen\ (\ 0\ g)}{F1xF2xF3xF4xF5}$$

11. PK CORRECTION

No PK correction was established as the bioavailability does not appear to be more than 40% difference as compared to estimation of a 100% bioavailability. For more data on the pharmacokinetic of the compound please refer to annex 1. Pharmacokinetic and Metabolism of Piroxicam.

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ANNEX 1: PHARMACOKINETICS AND METABOLISM OF PIROXICAM

The pharmacokinetic characteristics according to the most recent label (2010) for Feldene are the followings:

Absorption: Piroxicam is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses and generally peak within three to five hours after medication.

The prolonged half-life (50 hours) results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 µg/mL, while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg piroxicam, usually stabilize at 3–8 µg/mL. Most patients approximate steady state plasma levels within 7–12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

With food there is a slight delay in the rate but not the extent of absorption following oral administration. The concomitant administration of antacids (aluminum hydroxide or aluminum hydroxide with magnesium hydroxide) have been shown to have no effect on the plasma levels of orally administered piroxicam.

Distribution: The apparent volume of distribution of piroxicam is approximately 0.14 L/kg. Ninety-nine percent of plasma piroxicam is bound to plasma proteins. Piroxicam is excreted into human milk. In man it penetrates into the synovial fluid of patients with rheumatoid arthritis, osteoarthritis and re-active synovitis, where mean concentrations are approximately 40% of those in the plasma; it is also demonstrable in synovial tissues. The presence in breast milk has been determined during initial and long-term conditions (52 days). Piroxicam appeared in breast milk at about 1% to 3% of the maternal concentration. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment.

Metabolism: Metabolism of piroxicam occurs by hydroxylation at the 5 position of the pyridyl side chain and glucuro-conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. In vitro studies indicate cytochrome P4502C9 (CYP2C9) as the main enzyme involved in the formation to the 5'-hydroxy-piroxicam, the major metabolite (see Pharmacogenetics, and Special Populations, Poor Metabolizers of CYP2C9 Substrates). The biotransformation products of piroxicam metabolism are reported to not have any anti-inflammatory activity.

Higher systemic exposure of piroxicam has been noted in subjects with CYP2C9 polymorphisms compared to normal metabolizer type subjects (see Pharmacogenetics, and Special Populations, Poor Metabolizers of CYP2C9 Substrates).

Excretion: Piroxicam and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as in the feces. Approximately 5% of a piroxicam dose is excreted unchanged. The plasma half-life (T½) for piroxicam is approximately 50 hours.

Pharmacogenetics: CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from one published report that included nine subjects each with heterozygous CYP2C9*1/*2 and CYP2C9*1/*3 genotypes and one subject with the homozygous CYP2C9*3/*3 genotype showed piroxicam systemic levels that were 1.7-, 1.7- and 5.3-fold, respectively, higher compared to the 17 subjects with CYP2C9*1/*1 or normal metabolizer genotype. The pharmacokinetics of piroxicam have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups.

Special Populations

Pediatric: Piroxicam has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency: The effects of hepatic disease on piroxicam pharmacokinetics have not been established. However, a substantial portion of piroxicam elimination occurs by hepatic metabolism.

Consequently, patients with hepatic disease may require reduced doses of piroxicam as compared to patients with normal hepatic function.

Poor Metabolizers of CYP2C9 Substrates: Patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) should be administered piroxicam with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Renal Insufficiency: Piroxicam pharmacokinetics have been investigated in patients with renal insufficiency. Studies indicate patients with mild to moderate renal impairment may not require dosing adjustments. However, the pharmacokinetic properties of piroxicam in patients with severe renal insufficiency or those receiving hemodialysis are not known.