FASS

Aprovel

Sanofi AB

Tablett 75 mg

(Tillhandahålls ej) (vit till gråvit, bikonvex, oval med ett hjärta på en sida och 2771 på den andra)

Angiotensin II-antagonist

Aktiv substans:

Irbesartan

ATC-kod:

C09CA04

Läkemedel från Sanofi AB omfattas av Läkemedelsförsäkringen. Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Irbesartan

Miljörisk: Användning av irbesartan har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Irbesartan bryts ned långsamt i miljön.
Bioackumulering: Irbesartan har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}$ *A*(100-R)

PEC = 0.184 µg/L

Where:
A = 1342.937 kg (total sold amount API in Sweden year 2022, data from IQVIA)
R = 0% removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)
P = number of inhabitants in Sweden = $10*10^{6}$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA, 2008; Ref I).
D = factor of dilution of waste water by surface water flow = 10 (ECHA, 2008; Ref I).

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies
Algae (Pseudokirchneriella subcapitata):
EC_{50} 72 h (biomass): 79 000 µg/L
NOEC: 7200 µg/L
(Protocol: OECD 201)
(Ref II)

EC_{50} 72 h (growth inhibition): 460 000 µg/L

NOEC: 23 000 µg/L
(Protocol: OECD 201)
(Ref II)

Crustacean (Daphnia magna):
EC_{50} 48 h (immobilization): 191 000 µg/L
NOEC 48 h: 86 400 µg/L
(Protocol: FDA 4.08/OECD 202)
(Ref III)

EC_{50} 21 days (reduction in reproduction): 15 600 µg/L
NOEC 21 days (reduction in reproduction): 10 400 µg/L
LOEC 21 days (reduction in reproduction): 23 300 µg/L
(Protocol: OECD 211)
(Ref IV)

Fish (Oncorhynchus mykiss):
LC_{50} 96 h (mortality) > 290 000 µg/lL
(Protocol: OECD 203)
(Ref IV)

Fish (Pimephales promelas):
NOEC 28 days (growth): 7040 µg/L
(Protocol: OECD 210)
(Ref VI)

Other ecotoxicity data:
PNEC = 704 µg/L, lowest EC_{50}/10 using results from the most sensitive chronic toxicity endpoint and an assessment factor of 10 (Long-term results from at least three species of the base set), to

add a safety margin to the toxicity endpoint. The most sensitive species was *Pimephales promelas* for which the NOEC 28 days (growth) was 7040 µg/L.

Environmental Risk Classification (PEC/PNEC ratio)

PEC/PNEC= 0.184/704 = 0.000261, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase:
"Use of Irbesartan has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation
Ready degradability:
Test results showed 22.5 % degradation in 28 days (FDA 3.11/OECD 301)
(Ref VII)

Simulation studies
DT50 in water:
$DT50_{total\ system}$ = 8.7 (sediment 1) -12.5 (sediment 2) days. At the end of the study, there were 17.9% (sediment 1) and 23.9% (sediment 2) of parent compound remaining (in 100 days). Ambient extractions were carried out by shaking the sediment/solvent mixture at room temperature for 20 min. Reflux extraction was allowed to proceed for 4 h. The extract solution and sediment solids were separated by centrifugation. The non-extractable radioactivity in selected samples, where this was greater than 10 % of the applied radioactivity, was characterized using an acid/base fractionation procedure.
(Protocol: OECD 308)
(Ref VIII)

Abiotic degradation
Hydrolysis:
The half-life of Irbesartan was 40.1 days at pH 7, 25°C .
(Protocol: FDA 3.09/OECD111)
(Ref IX)

Photolysis:
Test showed a half-life of 6.41 h at pH 7.
(Protocol: FDA 3.10)
(Ref X)

Justification of chosen degradation phrase:
Irbesartan fails to pass the criteria for ready biodegradability. As $DT50_{total\ system}$ < 32 days with still more than 15 % of the parent compounds remaining at the end of the study, the correct phrase is:
“Irbesartan is slowly degraded in the environment”.

Bioaccumulation

Partition coefficient:
Log K_{ow} = 1.13 at pH 7 (OECD 107)
(Ref XI)

Justification of chosen bioaccumulation phrase:
Since log K_{ow} < 4 at pH 7, irbesartan has low potential for bioaccumulation.

Excretion (metabolism)

The substance is excreted almost exclusively as metabolites with only 2 % as unchanged.
(Ref XII)
Metabolites identified are (1) Tetrazole N2-beta-glucuronide conjugate of irbesartan, (2) monohydroxylated metabolite resulting from omega-1 oxidation of the butyl side chain, (3, 4) two different monohydroxylated metabolites resulting from oxidation of the spirocyclopentane ring, (5) a diol resulting from omega-1 oxidation of the butyl side chain and oxidation of the spirocyclopentane ring, (6) a keto metabolite resulting from further oxidation of the omega-1 monohydroxy metabolite, (7) a keto-alcohol resulting from further oxidation of the omega-1 hydroxyl of the diol, and (8) a carboxylic acid metabolite resulting from oxidation of the terminal methyl group of the butyl side chain.
(Ref XIII)
The pharmacological activity of the metabolites is not known.

References

I. ECHA, European Chemicals Agency, 2008 Guidance on information requirements and chemical safety assessment.
II. Sanofi, internal report: Irbesartan - Acute toxicity to the freshwater green alga, *Pseudokirchneriella subcapitata*. OECD 201. Report # 12534.6285. February 2006.
III. Sanofi, internal report: Static acute toxicity of Irbesartan (SR47436) to *Daphnia magna*. FDA 4.08. Report # 43075. July 1996.
IV. Sanofi, internal report: Prolonged toxicity to *Daphnia magna.* OECD 211. Report # BMY1106/064353. February 2007.

V. Sanofi, internal report: Irbesartan - Acute toxicity to rainbow trout *(Oncorhynchus mykiss)* understatic-renewal conditions. OECD 203. Report # 12534.6286. February 2006.
VI. Sanofi, internal report: Irbesartan - Fish early life stage toxicity test for fathead minnow. OECD 210. Report # BMY 1107. February 2007.
VII. Sanofi, internal report: Aerobic biodegradation in water using 14C-Irbesartan (SR47436). FDA 3.11. Report # 43090. July 1996.
VIII. Sanofi, internal report: Irbesartan – Aerobic transformation in aquatic sediment systems. OECD 308. Report # BMY 1266. July 2008.
IX. Sanofi, internal report: Hydrolysis as a function of pH of 14C-Irbesartan (SR47436). FDA 3.09. Report # 43092. August 1996.
X. Sanofi, internal report: Determination of the aqueous photodegradation of 14C-Irbesartan (SR47436). FDA 3.10. Report # 43089. August 1996.
XI. Sanofi, internal report: Determination of octanol/water partition coefficient (shake flask method) of Irbesartan (SR47436). FDA 3.02. Report # 43084. July 1996.
XII. Base de données publique des medicaments, Ministère des affaires sociales et de la santé, online consultation, March 2014: http://ec.europa.eu/health/documents/community-register/2013/2
XIII. Chando TJ, Everett DW, Kahle AD, Starrett AM, Vachharajani N, Shyu WC, Kripalani KJ, Barbhaiya RH. 1998. Biotransformation of Irbesartan in man. The American Society for Pharmacology and Experimental Therapeutics. 26 (5): 408-417.