FASS

Flutide® Diskus®

GlaxoSmithKline

Inhalationspulver, avdelad dos 50 mikrog/dos
(inhalationspulver)

Inflammationshämmande medel för inhalation vid astma och KOL

Aktiv substans:
Flutikasonpropionat

ATC-kod:
R03BA05

Läkemedel från GlaxoSmithKline omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Flutikasonpropionat

Miljörisk: Användning av flutikasonpropionat har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Flutikasonpropionat är potentiellt persistent.
Bioackumulering: Flutikasonpropionat 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 = 1.6 x 10^{-3} µg/L

Where:
A = 11.6695 kg (total sold amount API in Sweden year 2021, data from IQVIA).
R = 0% removal rate (conservatively, it has been assumed there is no 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 default) (Reference 1)
D = factor for dilution of wastewater by surface water flow = 10 (ECHA default) (Reference 1)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae:
No data

Water flea (Daphnia magna):
Acute toxicity
EC50 48 h (immobility) > 500µg/L (TAD 3.11/OECD 202) (Reference 3)

Chronic toxicity
No data

Fish (Pimephales promelas):
Acute toxicity
No data
Chronic toxicity
LOEC 116 days > 0.58 µg/L (OECD 210/234) (Reference 9)
NOEC = 0.58 µg/L

Other ecotoxicity data:
Microorganisms in activated sludge:
EC50 3 h (inhibition) > 1,000,000 µg/L @ 3 hrs (OECD 209) (Reference 4)
Earthworm *(Eisenia foetida):*
LC50 28 days (lethality) > 1000 mg/kg (TAD 4.12) (Reference 8)

PNEC = 0.58/10 = 0.058 µg/L

PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor applied for one long-term NOECs but where there is a high degree of confidence that the dataset includes the most sensitive species (fish) and addresses the specific mode of action (endocrine activity). On this basis the NOEC for fish has been used in the calculation.

PNEC Justification

According to the European Medicines Agency guideline on environmental risk assessment of medicinal products (EMA/CHMP/SWP/4447/00), use of Fluticasone propionate is unlikely to represent a risk for the environment, because the predicted

environmental concentration (PEC) is below the action limit 0.01 µg/L.

However, Fluticasone propionate is a glucocorticoid and, as such, is considered as a potential endocrine active substance. Fluticasone propionate is a generic drug but the related compound Fluticasone furoate (exclusive GSK pharmaceutical) was investigated for potential endocrine activity in an appropriate chronic vertebrate test system with relevant end points. Accordingly, GSK has conducted a fish early life-stage test, as per OECD 210, as a range-finder to set concentrations for an extended early life-stage test, exposing newly fertilised embryos until they reached sexual maturity (OECD 234). This study concluded that no statistically significant effects were observed between the controls and any of the test concentrations in terms of hatching success, post-hatch survival, growth, spawning ability or secondary sexual characteristics. Due to the mode of action of fluticasone furoate and its potential to act as an endocrine active substance there is a high degree of confidence that fish is the most sensitive species and on that basis there is a strong justification for applying an AF of 10 (Reference 1).

Proposed Read across between Fluticasone furoate and Fluticasone propionate

While these are distinct molecules there is nevertheless an appreciable similarity between the structural and physicochemical properties of both substances which warrants consideration when evaluating the suitability of a read across – see Table 1. Structurally, these compounds are similar and share many physiochemical properties. They differ only in the nature of the

17-α ester, having either a propionate or a furoate ester. It has been recognised that it is this ester that is important in determining activity at the glucocorticoid receptor. EC50 values for glucocorticoid receptor binding of fluticasone propionate and fluticasone furoate have been reported to be 1775 and 2989 respectively, which demonstrate while values are within the same order of magnitude, fluticasone furoate binds with greater affinity (Reference 11). The log kow values for both compounds are almost identical (2.78 and 2.61 for fluticasone propionate and fluticasone furoate, respectively) indicating uptake in the fish would be very similar.

In a GSK Non-Clinical studies a comparison of the in vitro pharmacology of fluticasone propionate and fluticasone furoate, in a number of assays, has been reported and the EC50 values shown to be in the same order of magnitude. In mammalian reproduction studies, although, different routes of exposure were used (subcutaneous and inhalation), both compounds show responses, in general, between 50-100 µg/kg/day dose ranges. However, NOAEL values were not provided for all studies to make more detailed comparisons.

To provide additional rational, for the testing of one compound, both compounds have been run through ECOSAR to derive QSAR data for ecotoxicological species. The data generated show a high similarity in the predicted effect concentrations between the two compounds, for common species used in ecotoxicology. While ECOSAR, of itself, is not sufficient support in favour of read across, it nonetheless indicates there are structural motifs and similarities between the two compounds which suggest that the rationale underpinning read across is not without foundation.

From the scientific peer-reviewed literature, Kugathas et al. (Reference 10) have shown, in vitro and in vivo, for a selected number of glucocorticoids, similar responses in fish in terms of plasma glucose concentrations and anti-inflammatory responses, with effect concentrations being as low as 0.1 µg/L. Currently, the PEC values based on IMS 2015 for Fluticasone furoate (0.00013 µg/L) and Fluticasone propionate (0.004 µg/L) in the European Union are known to be less than the action limit (0.01 µg/L) for both compounds.

In summary, both Fluticasone furoate and Fluticasone propionate have similarities in their structures and in their physiochemical properties. In vivo and in vitro responses are in the same order of magnitude, as are the predicted effect concentrations for ecotoxicity species. Findings in the published literature, testing nine of the most commonly synthetic glucocorticoids prescribed in the UK in 2006, have shown EC50 glucocorticoid receptor binding values within an order of magnitude, with Fluticasone furoate displaying greater receptor affinity. Importantly, the enhanced receptor sensitivity of Fluticasone furoate compared with Fluticasone propionate represents a more conservative endpoint for assessing environmental protection whilst minimizing additional testing on vertebrates. Accordingly, it is concluded that the results of the Fluticasone furoate extended life cycle fish study are applicable to the assessment of Fluticasone propionate.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = $1.6 \times 10^{-3} / 0.0058 = 0.28$, i.e. ≤ 0.1 PEC/PNEC ≤ 1 which justifies the phrase “Use of fluticasone propionate has been considered to result in insignificant environmental risk.”

Degradation

Biotic degradation

Ready degradability:
< 1.50% degradation in 28 days (TAD 3.11) (Reference 6)

Inherent degradability:
No Data

Soil Metabolism:
9-50% degradation in 64 days (OECD 307) (Reference 7)

Abiotic degradation

Hydrolysis:
No data

Photolysis:
No data

Justification of chosen degradation phrase:
Fluticasone propionate is not readily degradable or inherently degradable but it is slowly degraded in soil. The phrase "fluticasone propionate is potentially persistent" is thus chosen.

Bioaccumulation

Partitioning coefficent:
Log Kow = 2.80 at pH 7 (TAD 3.02). (Reference 5)

Justification of chosen bioaccumulation phrase:
Since log Kow < 4 at pH 7, the substance has a low potential for bioaccumulation.

Excretion (metabolism)

Fluticasone propionate does not persist in any tissue, and does not bind to melanin. The major route of metabolism is hydrolysis of the S-fluoromethyl carbothioate group, to yield a carboxylic acid (GR36264), which has very weak glucocorticoid or anti-inflammatory activity. In all test animal species, the route of excretion of radioactivity is independent of the route of administration of radiolabelled fluticasone propionate. Excretion is predominantly faecal and is essentially complete within 48 hours.

In man too, metabolic clearance is extensive, and elimination is consequently rapid. Thus drug entering the systemic circulation via the skin, will be rapidly inactivated. Oral bioavailability approaches zero, due to poor absorption and extensive first-pass metabolism. Therefore systemic exposure to any ingestion of the topical formulation will be low (Reference 2).

PBT/vPvB assessment

Fluticasone propionate does not fulfil the criteria for PBT and/or vPvB

All three properties i.e. 'P', 'B' and 'T' are required in order to classify a compound as PBT (Reference 1). Fluticasone propionate does not fulfil the criteria for PBT and/or vBvP based on log Pow < 4.

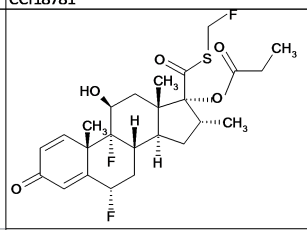
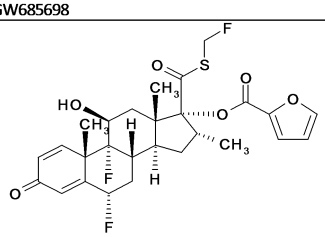
Please, also see Safety data sheets on http://www.msds-gsk.com/ExtMSDSlist.asp.

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Table 1 Comparison of fluticasone propionate with fluticasone furoate

	fluticasone propionate	**fluticasone furoate**
	CCI18781	GW685698
Structure		
Molecular formula	C25-H31-F3-O5-S	C27-H29-F3-O6-S
R phrases	R48/20/21/61/62	R48/20/21/61/62
Water solubility	0.0695 mg/l 25°C	0.3 mg/l measured
pH of aqueous solutions	Cannot be determined	4.4-4.5 at 10% suspension at 20°C
Hydrolysis	Chemically stable in water	Chemically stable in water
Biodegradation	Not readily biodegradable, but is inherently biodegradable. Not expected to persist in the env.	Not readily or inherently biodegradable and may persist in the env.
Aerobic	Ready: <44%, 28 day. Soil: 9-50%, 64 days	Inherent: 0% 28 days. Soil: 2-3%, 64 days
Log kow	2.78	2.61
Pharmacological effect	Selective glucocorticoid receptor agonist	Selective glucocorticoid receptor agonist
Oral toxicity:		
Acute: rat	LD50: >1000 mg/kg	LD50: >2000 mg/kg
Inhalataion toxicity:		
Acute: rat		Lethal conc: >0.133 mg/L
Repeat dose: rat	NOAEL 0.2 mcg/L/day (28 day)	NOAEL 3 mcg/L/day (26 week)
Skin effects	Irriration not expected following direct skin contact	Irritation not expected following direct skin contact
Eye effects	Irritation not expected following direct eye contact	Irritation not expected following direct eye contact
Sensitisation	Allergic reactions might occur following repeated contact	No evidence of respiratory allergy from lab studies
Genetic toxicitcy	Not expected to be genotoxic	Not expected to be genotoxic
Carcinogenicity	Not listed as a carcinogen	Not listed as a carcinogen
Repro effects (human)	Known/presumed to cause toxicity to developing offspring	Known/presumed to cause toxicity to developing offspring
	Possible risk of impaired fertility to humans	Possible risk of impaired fertility to humans
Mammalian studies		
Reproduction	Mice, subcutaneous: 150 ug/kg/day maternally toxic dose. Reduction in maternal body weight gain, induction in cleft palate.	
	Rats: 100 ug/kg/day maternal toxicity, embryo growth retardation, omphalocoele.	Female rats, inhalation: <91 ug/kg/day: No adverse effects on mating performance, precoital interval, fertility, major skeletal or visceral abnormalities. 91 ug/kg/day: adverse effects on maternal weight gain and food intake, higher incidence of prolonged oestrus cycles. Increased incidence of foetuses with incompletely ossified sternebra at high dose + lower foetal weight. No effects at 23 ug/kg/day.
	Male rats, subcutaneous: 50 ug/kg/day increase to 100 ug/kg/day did not affect fertility, mating performance in F0 and F1 generation. Dose related effects seen on growth	Male rats: No effects on fertility <29 ug/kg/day by inhalation.
	Rabbits, subcutaneous: <300 ug/kg/day incompatible with sustained pregancy. Oral doses no effect	Rabbits, inhalation: 47 ug/kg/day and above = maternal weight loss and abortion. <8ug/kg/day in definitive study = initial maternal weight loss, but no adverse effects on embryofoetal development
Repro and dev	Rats, subcutaneous: <50 ug/kg/day. 50 ug/kg/day = reduction in maternal body weight gain. No effect on development of offspring.	Rats: 82, 94.4 and 94.9 ug/kg/day = foetal growth retardadation. NOAEL for embryofoetal dev: 29.5 ug/kg/day
Ecotoxicity data:		
Activated sludge respiration	IC50: >1000 mg/l 3 hrs activated sludge	IC50: >1000 mg/l 3 hrs activated sludge (nominal)
Daphnid	No toxicity to daphnids, but upper range limited due to low water solubility	No toxicity to daphnids, but upper range limited due to low water solubility
	EC50: >0.55 mg/l 48 hrs, static	EC50: >4.2 mg/l 48 hrs, static renewal; NOEC 4.2 mg/l
Fish	No data	EC50; >10 mg/l 96 hrs, QSAR estimate
Earthworm	Not toxic to earthworms	Not toxic to earthworms
	EC50: >1000 mg/kg, 28 days	EC50: >1000 mg/kg, 28 days, NOEC 1000 mg/kg

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