Review of International Risk Assessment of Zilpaterol (including JECFA Assessments)

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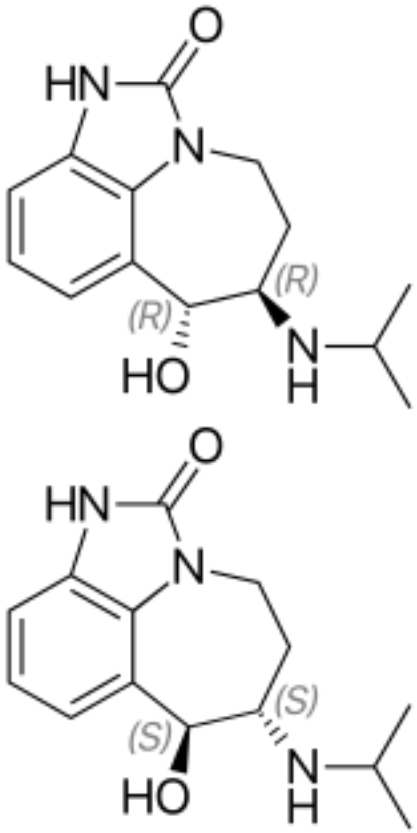
Overview

- Zilpaterol (Zilmax®) - for increased weight gain, improved feed efficiency and increased carcass leanness in cattle fed in confinement during the last 20 to 40 days on feed; not permitted for use in lactating dairy cattle
- β2-adrenergic agonist activity (binds to the receptor); in humans, β2-adrenergic agonists cause smooth muscle relaxation of bronchial passages, vasodilation in muscle and liver, relaxation of uterine muscle, and release of insulin. Used to treat asthma and pulmonary diseases.
- Zilpaterol hydrochloride has been assessed by JECFA at its 78th (2014) and 81st (2015) meetings at the request of the CCRVDF21 and CCRVDF22.



JECFA – Zilpaterol HCl

- 78th JECFA initially established an ADI of 0.04 ug/kg bw; no issue with the safety assessment but questions remained re. residue data on which to recommend MRLs
- Full toxicological data package was available for evaluation (PBPK, short term, long term, cancer bioassays, developmental, reproductive, genotoxicity)
- The most sensitive effect was considered to be neurological (tremors); observed in human volunteers at a LOAEL of 0.76 ug/kg bw (described as slight and transitory)
- Application of a 20-fold UF gave the ADI of 0.04 ug/kg bw or an acceptable daily intake of 2.4 ug for a 60 kg person
- At the 81st JECFA, additional residue data on bioavailability and depletion was made available; in addition, as the critical study used to set the ADI was acute dosing, it was considered appropriate to set an ARfD

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JECFA – Zilpaterol HCl (2)

- Main tissues are liver < kidney <<< muscle < fat; after a 48 hr withdrawal period, residues only detected in liver and kidney
- The MRLs recommended by JECFA for bovine tissues are based on an acute dietary exposure scenario (GEADE). Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs
- 95th percentile of residue concentrations in bovine tissues at the 72-hour time point: 4.1 µg/kg in kidney, 4.3 µg/kg in liver and 0.6 µg/kg in muscle = 99% of ARfD for the general population and 117% for children.
- Considered a refined assessment with 95% residues derived at 77 hours post-dose: 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.
- GEADE of 1.9 µg/day (80% of the ARfD) for the general population and 0.57 µg/day for children (94% of the ARfD)
- It was noted that the time point at which the MRLs are calculated (77 hours) is consistent with currently approved withdrawal times (GVP).

JECFA

The Joint FAO/WHO
Expert Committee on Food Additives

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JECFA Summary

- Oral bioavailability of zilpaterol is high (almost 100%); Cmax reached within 1 hr. and similar PBPK profiles are seen with acute and repeat dosing; T1/2 humans is 3-4 hours.
- Short term GLP studies conducted in rodents (rats and mice), dogs, Cynomolgus monkeys, microswine and cattle
- Rats – decreased average HR at a LOAEL of 50 ug/kg bw/day (13 weeks); NOAEL (52 weeks) = 50 ug/kg bw/day. Monkeys - NOAEL was 10 ug/kg bw per day (4 weeks), based on reduced blood pressure; increased heart rate with a decreased QT interval at 50 ug/kg bw per day
- No evidence for reproductive or developmental toxicity (rodents) at dose up to 1 mg/kg bw/day; embryo and fetal toxicity only observed at doses > 10 mg/kg bw/day
- Humans – 0.25 mg/person (3.6 ug/kg bw) NOAEL for diastolic blood pressure, stroke volume, heart rate, bronchodilatation and tremor; LOAEL for increased heart rate (5.75 bpm) and increased blood glucose
- Asthma – 0.05 mg/person (0.76 ug/kg bw) bronchodilation NOAEL, tremor LOAEL.
- Observed effects were slight and transitory and typically related to the β2-adrenergic agonist activity of zilpaterol HCl

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FDA - 2006

- The lowest short-term No-Observed-Adverse-Effect Level (NOAEL) of 10 µg/kg bw per day was found in monkeys (reduced blood pressure, increased heart rate associated with decreased QT intervals at 50 µg kg/bw per day for 4 weeks).
- When zilpaterol was given to rats for 1 year, reversible effects on heart rate and blood pressure resulted in a NOEL of 250 µg/kg bw per day
- Human studies – single doses of $\geq$ 4.14 µg/kg bw caused HR and blood glucose increases; doses $\geq$ 8.33 µg/kg bw caused tremors, with the NOEL being 1.7 µg/kg bw.
- FDA – most sensitive effect was bronchodilation in people with asthma, with the NOEL being 0.83 ug/kg bw; ADI was set at 0.083 µg/kg bw. Bronchodilation was described as slight, transitory and reversible at the next highest dose (1.7 µg/kg bw)

FDA U.S. FOOD & DRUG ADMINISTRATION

EFSA - 2016

- JECFA derived an Acute Reference Dose and an Acceptable Daily Intake of 0.04 µg/kg body weight (per day) based on neurological effects seen in humans (tremors) and, after carrying out an exposure assessment, has recommended maximum residue limits (MRLs) for zilpaterol in cattle of 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.
- The LOAEL and UF used by JECFA are “reasonable” except EFSA may have conducted DR modeling
- The approach followed by JECFA for setting MRLs for zilpaterol appears to be scientifically robust*
- Only a withdrawal period of more than 3 days would result in residue levels leading to acute dietary exposure estimates below the ARfD
- The available literature investigating the effects of zilpaterol on animal health and welfare is limited but indicates** a potential increase in mortality, heart rate, respiration rate and agonistic behaviour in cattle.

efsa
European Food Safety Authority


thank you
merci
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
obrigado
dziękuję
bedankt
go raibh maith agat
mochchakkeram
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