GLOBAL FOOD REGULATORY SCIENCE SOCIETY

Review of

International Risk Assessment of Zilpaterol

(including JECFA Assessments)

Contents

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Background

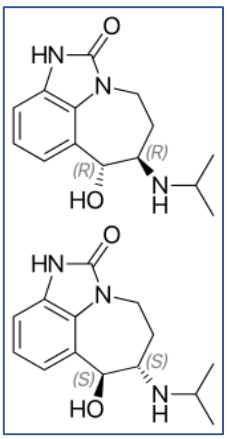
This review offers a general summary of the scientific assessments carried out in relation with the substance Zilpaterol, for which Maximum Residue Levels (MRLs) were developed by the Codex Alimentarius Commission, under the auspices of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVF), which are considered for adoption by the 45th Session of the Codex Alimentarius Commission (CAC45).

Zilpaterol (commercialized as Zilmax®) is a substance used in food producing animals with the intent to support weight gain, improved feed efficiency and increased carcass leanness in cattle fed in confinement during the last 20 to 40 days on feed. This substance is not permitted for use in lactating dairy cattle.

Zilpaterol features a β2-adrenergic agonist activity. 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. This substance has been used to treat asthma and pulmonary diseases in humans.

Assessments by the FAO/WHO Joint Expert Committee on Food Additives:

Zilpaterol hydrochloride was assessed by JECFA at its 78th (2014) and 81st (2015) meetings at the request of the CCRVDF21 and CCRVDF22.



The 78th JECFA initially established an ADI of 0.04 microgram/kg bw and did not identify safety assessment issues. However, questions remained in relation with the analytical methods and associated residue data on the basis of which MRLs are to be recommended.

A fulsome toxicological data package was used for this evaluation and included information on Physiologically Based Pharmacokinetics (PBPK), short term and long term toxicity, cancer bioassays, developmental and reproductive toxicity as well genotoxicity.

Studies included information derived from experimentations on rodents (rats and mice), dogs, Cynomolgus monkeys, microswine and cattle.

There was no evidence for reproductive or developmental toxicity (in rodents) at dose up to 1 mg/kg bw/day; Embryo and fetal toxicity were only observed at doses higher than 10 mg/kg bw/day.

Attempts to derive Health Based Guidance Values (HBGVs) relied on information stemming from several animal species with the following effects observed:

- Decreased average Heart Rate **with Rats** at a LOAEL of 50 micrograms/kg bw/day (13 weeks); NOAEL (52 weeks) = 50micrograms /kg bw/day.
- Reduced Blood Pression and increased heart rate **with Monkeys** leading to a NOAEL estimated at 10 micrograms/kg bw per day (4 weeks).

- In Humans, a NOAEL of 0.25 mg/person (3.6 micrograms/kg bw) based on diastolic blood pressure, stroke volume, heart rate, bronchodilatation and tremor; the observed effects in humans were identified as slight and transitory and typically related to the β2-adrenergic agonist activity of zilpaterol HCl.

The most sensitive effect was considered to be neurological (tremors) which was observed in human volunteers at a LOAEL of 0.76 micrograms/kg bw. This effect was also described as slight and transitory.

The application of a 20-fold Uncertainty Factor (UF) led to the **ADI of 0.04 microgram/kg bw** or an **acceptable daily intake of 2.4 microgram** for a 60 kg person.

At the 81st JECFA, additional residue data on bioavailability and depletion were made available. In addition, it was considered that the critical study used to set the ADI was indicative of acute dosing and therefore conducive to establish an Acute Reference Dose (ARfD).

While the main tissues targeted were the liver, kidney, muscle and fat, a 48h withdrawal period showed that residues were only detected in liver and kidney

The MRLs recommended by JECFA for bovine tissues were based on an acute dietary exposure scenario, referring to the Global Estimate of Acute Dietary Exposure (GEADE):

- The 95th percentile of residue concentrations in bovine tissues at the 72-hour time point were 4.1 µg/kg in kidney, 4.3 µg/kg in liver and 0.6 µg/kg in muscle which represent 99% of ARfD for the general population and 117% for children.
- A refined assessment showed that 95% residues derived at 77 hours post-dose at the levels of 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle. This leads to a 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).

Assessments by Other Agencies

The US Food and Drug Administration (US FDA) - 2016

In 2016, the US FDA established the lowest short-term No-Observed-Adverse-Effect Level (NOAEL) of 10 µg/kg bw per day was based on observations in monkeys (based on reduced blood pressure, increased heart rate associated with decreased QT intervals at 50 µg kg/bw per day for 4 weeks).

The US FDA review also established that 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 reviewed by the US FDA included the reliance on single dose experimenting with a dosing higher than 4.14 µg/kg bw, which was found to cause Heart Rate and blood glucose increases; doses higher than 8.33 µg/kg bw caused tremors, with the NOEL being 1.7 µg/kg bw.

The US FDA considered that most sensitive effect was bronchodilation in people with asthma, with the NOEL being 0.83 ug/kg bw. As a result, the 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)

European Food Safety Authority (EFSA) - 2016

EFSA reviewed the JECFA assessment including:

- The derived Acute Reference Dose as well as the Acceptable Daily Intake of 0.04 µg/kg body weight (per day) based on neurological effects seen in humans (tremors) and,
- The exposure assessment, which led to the recommendation of 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.

EFSA concluded that the LOAEL and UF used by JECFA are "reasonable" and that the overall approach followed by JECFA for setting MRLs for zilpaterol "appears to be scientifically robust".

EFSA commented that the available literature investigating the effects of zilpaterol on animal health and welfare is limited but may indicate a potential increase in mortality, heart rate, respiration rate and agonistic behaviour in cattle.

EFSA finally concluded a withdrawal period of more than 3 days would result in residue levels leading to acute dietary exposure estimates below the ARfD.

Conclusion

The assessment conducted by JECFA is the only reference that Codex relies upon to set food safety standards such as MRLs. The safety assessment conducted by JECFA enabled to set conditions of use of Zilpaterol that allows the safety of tissues where residues may be detected if MRLs are respected.

The JECFA assessment was not subject to a concern expressed by members of Codex and further supported by other assessments carried out by other food regulatory and risk assessment bodies, leading to establish safe conditions of use of Zilpaterol in Cattle and to support the relevance and robustness of the proposed Codex MRLs for Zilpaterol in Cattle tissues: 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.

Zilpaterol is approved for use in several countries, including in Canada, the United States, south Africa, Korea, Mexico, Panama, Ukraine, Brazil and Lebanon. Record of sale and use show important use in South Africa, Mexico, Panama, Costa Rica, Lebanon, Guatemala, Honduras, Lesotho and Nicaragua.