PRODUCT MONOGRAPH

ZADITEN®

(ketotifen fumarate)

Tablets 1 mg

Syrup 1 mg/5 mL

Pediatric Asthma Prophylactic
and Antiallergic Agent

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PRODUCT MONOGRAPH

NAME OF DRUG

ZADITEN®
(ketotifen fumarate)
Tablets 1 mg
Syrup 1 mg/5 mL

THERAPEUTIC CLASSIFICATION

Pediatric Asthma Prophylactic and Anti-Allergic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Ketotifen (ketotifen fumarate) is a non-bronchodilator anti-asthmatic drug which inhibits the effects of certain endogenous substances known to be inflammatory mediators, and thereby exerts anti-allergic activity. Preclinical studies indicated that Zaditen's anti-H_1 effect seems to be distinct from its anti-allergic properties.

The effectiveness of Zaditen in the chronic management of mild atopic pediatric asthma has been shown in clinical trials. Continued use of Zaditen results in a partial reduction in the frequency, severity and duration of asthma symptoms and attacks, and may lead to the reduction in the daily requirements of concomitant anti-asthmatic medication such as theophyllines and β_2-agonists, without the deterioration in pulmonary function (FEV_1, FVC and PEFR). Clinical improvements have been observed in some cases within the first weeks of treatment and generally reach statistical significance after ten weeks. Zaditen may have an anti-inflammatory effect in the lungs and the time of onset of clinical efficacy may reflect the recovery period of the lungs from inflammation.

Pharmacological studies have revealed a number of properties of ketotifen fumarate which may contribute to its anti-allergic activity and its ability to affect the underlying pathology of asthma:

In Vivo Results

- Inhibition of the development of airway hyperreactivity associated with activation of platelets by PAF (Platelet Activating Factor) or caused by neural activation following the use of sympathomimetic drugs or the exposure to allergen.

- Inhibition of PAF-induced accumulation of eosinophils and platelets in the airways.

- Suppression of the priming of eosinophils by human recombinant cytokines and thereby suppression of the influx of eosinophils into inflammatory loci.

- Antagonism of bronchoconstriction due to leukotrienes.

In Vitro Results

- Inhibition of the release of allergic mediators such as histamine, leukotrienes C_4 and D_4 (SRS-A) and PAF.

In addition, ketotifen fumarate is a potent anti-allergic substance possessing a powerful and sustained non-comptetitive histamine (H_1) blocking property.

In humans, the absorption of ketotifen fumarate from an oral administration was demonstrated to be at least 60%, and possibly even greater. The rate of absorption of ketotifen fumarate in humans was assessed as rather rapid, since the plasma concentration reached its maximum 3 hours after oral administration; the absorption half-life was calculated to be 1 hour. Bioavailability amounts to approximately 50% due to a large first pass effect. Maximum plasma concentrations are reached within 2-4 hours. The percentage of protein binding in humans is 75% and is also concentration-independent. Ketotifen fumarate is eliminated biphasically; there are two disposition half-lifes of 3-5 hours and 21 hours for distribution and disappearance phases respectively. Within 48 hours, urinary excretion amounts to 1% as unchanged drug and 60-70% as metabolites.

The main metabolite in the urine is the inactive ketotifen-N-glucuronide. The bioavailability of the various forms of Zaditen is not influenced by the intake of food.

The pattern of metabolism in children is the same as in adults, but the clearance is higher in children. Children over the age of 3 years therefore require the same daily dosage regimen as adults. In infants aged less than 3 years, however, the dosage must be adjusted, since the mean levels of the drug in infants are higher than those found in children, when the same dose is given.

INDICATIONS AND CLINICAL USE

Zaditen (ketotifen fumarate) is indicated as an add-on medication in the chronic treatment of mild atopic asthmatic children.

Zaditen is a prophylactic agent to be used on a continuous basis and is not effective in the acute prevention or treatment of acute asthma attacks. Continuous use of Zaditen may reduce the frequency, severity and duration of asthmatic symptoms or attacks, and lead to a reduction in daily requirements of concomitant anti-asthmatic medication, like theophyllines and β_2-agonists.

Several weeks of Zaditen therapy may be necessary before the therapeutic effect becomes clinically evident. Full clinical effectiveness is generally reached after 10 weeks of treatment. Zaditen may have an anti-inflammatory effect in the lungs and the time of onset of clinical efficacy may reflect the recovery period of the lungs from inflammation. It is therefore recommended that for patients not adequately responding within a few weeks, treatment with Zaditen should be maintained for a minimum of 2 to 3 months. If it is necessary to withdraw Zaditen, this should be done progressively over a period of 2 to 4 weeks. Symptoms of asthma may recur.

CONTRAINDICATIONS

Known hypersensitivity to ketotifen or any other components of the formulations. Patients sensitive to benzoate compounds should not take Zaditen syrup.

PRECAUTIONS

General

Symptomatic and prophylactic anti-asthmatic drugs (xanthine derivatives, β_2-agonists, sodium cromoglycate, corticosteroids) already in use should not be reduced immediately when treatment with Zaditen (ketotifen fumarate) is initiated. This applies especially to systemic corticosteroids and ACTH injections because of the possible existence of adrenocortical insufficiency in steroid-dependent patients; in such cases recovery of a normal pituitary-adrenal response to stress may take up to one year.

Convulsions

Convulsions have been reported very rarely during Zaditen therapy. As Zaditen may lower the seizure threshold it should be used with caution in patients with a history of epilepsy.

Occupational

Since drowsiness may occur in the early stages of therapy, patients engaging in activities requiring rapid and precise responses should be cautioned.

Drug Interactions

A reversible fall in the thrombocyte count in patients receiving Zaditen concomitantly with oral antidiabetic agents has been observed in rare cases. Thrombocyte counts should therefore be carried out in patients taking oral antidiabetic agents concomitantly.

Zaditen may potentiate the effects of sedatives, hypnotics, antihistamines and alcohol.

Use in Obstetrics

Although ketotifen was without effect on pregnancy and on peri- and post-natal development at dose levels which were tolerated by the mother animals, its safety in human pregnancy has not been established. Zaditen should therefore be given to pregnant women only in compelling circumstances.

Nursing mothers

Ketotifen is excreted in rat milk. It is assumed that this drug is also excreted in human breast milk, and therefore mothers receiving Zaditen should not breast-feed.

Patients with Special Diseases and Conditions

Zaditen syrup should not be administered to patients sensitive to benzoate compounds. Zaditen tablets are benzoate-free and can be administered alternatively to such patients.

In diabetic patients, the carbohydrate content of the syrup (5 ml - 4 g carbohydrate) should be taken into consideration.

ADVERSE REACTIONS

The following table illustrates the adverse reactions which were reported in a Canadian Multicentre Trial involving 196 asthmatic children aged 5 to 17 years. This double-blind, placebo controlled study lasted 30 weeks.

REPORTED ADVERSE REACTIONS

System	Reaction	Incidence (%) Zaditen (n=75)	Placebo (n=78)
CNS	Sedation	8.0	9.0
	Irritability	0	1.3
	Headache	1.3	1.3
	Dizziness	0	2.6
	Fainting	0	1.3
	Tingling in legs	0	1.3
	Sleep disturbance	1.3	0
GI	Diarrhea	0	2.6
	Nausea	0	1.3
	Vomiting	0	2.6
	Weight gain	5.3	1.3
	Increased appetite	1.3	0
	Abdominal pain	1.3	0
Skin	Rash	4.0	1.3
	Urticaria	1.3	1.3
Infections	Ear	1.3	2.6
	Flu	2.6	1.3
	Respiratory	4.0	0
	Fever	0	2.6
Misc.	Nose bleed	1.3	0
	Puffy eyelid	1.3	0
	Blood in stool	0	1.3
	Hypertension	0	1.3

There was a relatively low incidence of adverse reactions reported. These were similar in both the Zaditen (ketotifen fumarate) and placebo treated groups of patients. The reports for CNS and GI symptoms in the placebo group are side effects known to be associated with xanthine administration, which was being used concomitantly by some patients during the study.

Thrombocytopenia has been reported when Zaditen (ketotifen fumarate) is combined with oral hypoglycemic agents (see PRECAUTIONS).

Occasional, isolated, instances of elevated liver enzymes levels have been seen during clinical trials. No definite relationship to ketotifen fumarate therapy has been established.

Sedation and, rarely, dry mouth or slight dizziness may occur at the beginning of treatment, but usually disappear spontaneously with continued medication. Occasionally, symptoms of CNS stimulation, such as excitation, irritability, insomnia and nervousness have been observed, particularly in children. Weight gain has also been reported.

Cystitis has been rarely described in association with Zaditen. Very rarely Zaditen may cause an increase in liver enzymes and hepatitis. Isolated cases of severe skin reactions (erythema multiforme, Stevens Johnson syndrome), have been reported, the occurrence being approximately 1 case in 2 million patients exposed to Zaditen.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosages with up to 120 mg Zaditen (ketotifen fumarate) have been reported. The main symptoms of acute overdosage include: drowsiness to severe sedation; confusion and disorientation; tachycardia and hypotension; convulsions, especially in children; hyperexcitability in children; reversible coma. Treatment should be symptomatic. If ingestion is very recent, emptying of the stomach may be considered. Administration of activated charcoal may be beneficial. If necessary, specific or symptomatic treatment and monitoring of the cardiovascular system and physostigmine for anticholinergic effects are recommended; if excitation or convulsions are present, short-acting barbiturates or benzodiazepines may be given.

DOSAGE AND ADMINISTRATION

In children older than 3 years of age, Zaditen (ketotifen fumarate) should be given at a dose of 1 mg twice daily in the morning and evening.

In children from 6 months to 3 years: 0.05 mg (= 0.25 mL of syrup) per kilogram body weight given twice daily, morning and evening.

To minimize the initial sedation with Zaditen, a slow increase in dosage is recommended during the first week of treatment commencing with one half the daily recommended dosage given in 2 divided doses or in a single dose given in the evening, followed within 5 days, by an increase to the full therapeutic dose.

Concomitant Therapy

Existing asthma therapy should be maintained. A progressive reduction in dosage of other asthma drugs, where clinically indicated, should be attempted only after 6-12 weeks of Zaditen therapy.

Reduction of Corticosteroids

It is not fully established, but some patients may be able to reduce corticosteroids.

The reduction in the daily maintenance dosage of steroids should be stepwise according to the recommended methods. The gradual reduction should be continued until either the patient cannot tolerate a further reduction, or it is found possible to withdraw corticosteroids completely.

If troublesome symptoms recur during the period of reduction, the daily dose of corticosteroids should be raised immediately. A larger increase in the steroid dose may be essential at times, as a temporary measure, to control a severe relapse induced by antigen challenge, infection or stress. (The increased physical or mental activity resulting

from subjective improvement can also constitute a stress.) When symptoms are brought under control, a progressive reduction may be attempted as before.

Any reduction should be gradual while maintaining close surveillance and frequent examination of the patient. The ability of these patients to react to stress is usually impaired. Acute adrenal insufficiency and severe asthma can be precipitated by an increase in stress and/or reduction of either steroid or ACTH therapy. It is advisable to assess adrenal and pituitary function before reducing steroid dosage in patients who have received long-term therapy.

Method of Withdrawing ACTH

The same principles as discussed above.

PHARMACEUTICAL INFORMATION

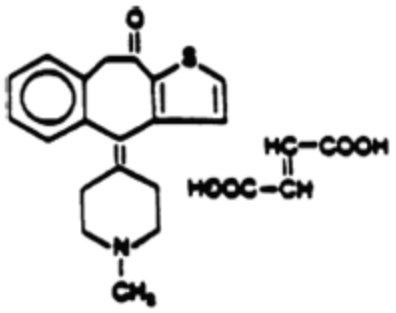
Drug Substance

Trade Name: Zaditen

Generic Name: ketotifen fumarate

Chemical Name: 4-(1-methyl-4-piperidylidene)-4H-benzo [4,5] cyclohepta [1,2-b] thiophene-10 (9H)- one hydrogen fumarate

Structural Formula:



Molecular Formula: $C_{19}H_{19}NOS + C_4H_4O_4$

Molecular Weight: 425.5

Description: Fine crystalline, yellowish gray powder with a faintly bitter taste. In the form of the hydrogen fumarate it is readily soluble in water. The active ingredient is stable in slightly acidic solution.

pKa-Value

Ka I = 8.43 ± 0.11

Estimated with ketotifen base by linear extrapolation with values from 5 different mixtures in ethanol/water.

Partition Coefficient

Chloroform/hydrochloric acid 0.1 N	1.2 : 1
n-Octanol/hydrochloric acid 0.1 N	0.7 : 1
Chloroform/phosphate buffer pH 6.8, 0.05 M	>100 : 1
n-Octanol/phosphate buffer pH 6.8, 0.05 M	>100 : 1

Melting Point

Ketotifen hfu melts with decomposition at about 190°C. Ketotifen hfu with 2.5 H_2O melts at approximately 130°C (ref. 1).

Composition

Tablets: Corn Starch, Ketotifen Fumarate, Lactose Monohydrate, Magnesium Stearate.

Syrup: Alcohol, Citric Acid, Ketotifen Hydrogen Fumarate, Methyl p-hydroxybenzoate, Propyl-p-hydroxybenzoate, Sodium Phosphate, Sorbitol Solution, Sucrose, Strawberry Flavor, Water.

Stability and Storage Recommendations

Tablets: Store at temperatures not exceeding 25°C, in a dry place.
Syrup: Store at temperatures not exceeding 25°C.

AVAILABILITY OF DOSAGE FORMS

Zaditen (ketotifen fumarate) Tablets

Each scored white tablet embossed with the name "ZADITEN" contains: 1 mg ketotifen. Tablets are to be swallowed. Available in packs of 56 tablets containing 4 blister strips of 14 tablets each.

Zaditen (ketotifen fumarate) Syrup

5 mL of syrup contain 1 mg ketotifen. Available in 250 mL bottles. To be administered orally.

INFORMATION FOR THE PATIENTS/PARENTS

Zaditen is a type of asthma medication which, when taken every day by mouth, may reduce the frequency, severity and duration of asthma symptoms or attacks in children.

Your physician will have prescribed Zaditen if your child's asthma is not well controlled, or to allow a reduction in your child's daily use of other anti-asthma medications.

Zaditen is taken orally twice a day. Zaditen does not provide relief for an acute attack, so that inhaled bronchodilator medication will still be required for rapid relief of symptoms when a severe attack occurs.

Remember:

- In case of deterioration, you should contact your doctor immediately.

- This medication has been prescribed for your child's current medical problem only. It must not be given to other people or used for other problems unless otherwise directed by your doctor.

- Like all medicines, Zaditen should be kept out of reach of small children.

- Do not discontinue using this medicine without first consulting with your doctor, and if you would like more information about this medicine, ask your doctor, nurse, or pharmacist.

Before Using this Medicine

In order to decide on the best treatment, your doctor should be told if your child:

- has had any unusual or allergic reaction to Zaditen, benzoates or any of the product constituents (see Product Ingredients)

- is taking any oral anti-diabetic medication.
- has a history of epilepsy.

Zaditen should not be used by anyone who is pregnant or breast-feeding a baby.

Proper Use of this Medicine

Since Zaditen interferes gradually with the chain of events leading to an asthma attack, at least 10 weeks of continuous use may be required before you and your physician can establish that it is effectively reducing your child's asthma symptoms.

Since Zaditen works continuously to prevent asthma attacks, you should find that in time your child's symptoms become less severe and inhaled bronchodilators are needed less frequently. As your child's asthma improves, it is necessary to keep taking Zaditen, and to consult your physician if and when you feel other asthma medications can be reduced.

Side Effects of this Medicine

Along with its beneficial effect, Zaditen may occasionally cause some unwanted effects. Side effects which may occur usually do not require medical attention; these include sedation, weight gain, rash, irritability, nervousness, dryness of the mouth, dizziness, nausea and headaches. If any side effect becomes bothersome, consult with your physician.

The drowsiness which occurs in some patients at the start of treatment with Zaditen is usually temporary and disappears as your child adjusts to the medication. The drowsiness may be worse if Zaditen is taken with sedatives, hypnotics, antihistamines or alcohol. If drowsiness occurs, children may have trouble with activities requiring mental alertness, and older children should not drive a car or operate dangerous machinery.

Rarely, inflammation of the bladder may occur. Very rarely Zaditen may cause an increase in liver enzymes and inflammation of the liver. Isolated cases of severe skin reactions have been reported.

Product Ingredients

Tablets: Corn Starch, Ketotifen Fumarate, Lactose Monohydrate, Magnesium Stearate.

Syrup: Alcohol, Citric Acid, Ketotifen Hydrogen Fumarate, Methyl p-hydroxybenzoate, Propyl-p-hydroxybenzoate, Sodium Phosphate, Sorbitol Solution, Sucrose, Strawberry Flavor, Water.

PHARMACOLOGY

Pharmacodynamics

The therapeutic action of Zaditen (ketotifen fumarate) on the symptoms of asthma and the impaired pulmonary function can be ascribed to a variety of pharmacological properties. Ketotifen fumarate inhibits in human tissue the in vitro release of a number of myotonic and inflammatory mediators, such as leukotrienes and histamines, as well as the in vivo release of NCF.

In vitro animal studies have shown that ketotifen fumarate produces a concentration dependent inhibition of stimulated histamine release from rat peritoneal mast cells, histamine induced contraction of isolated guinea pig ileum, and inhibits the induced release of SRS-A and histamine from sensitized guinea pig lungs.

In vitro studies of human tissue have shown similarly that ketotifen fumarate pretreatment of passively sensitized isolated leukocytes, and ketotifen fumarate treatment of lung tissue and basophils, produce a dose dependent inhibition of histamine and SRS-A after IgE-mediated challenge.

In vivo animal studies have shown that ketotifen fumarate also inhibits the action of mediators including a strong and persistent H-1 receptor blocking action resulting in protection of guinea pigs against the lethal effects of high doses of histamine and an inhibition of bronchospasms produced by histamine aerosol. Ketotifen fumarate inhibits in guinea pigs the bronchoconstriction elicited by leukotrienes (SRS-A) and the bronchial hyperreactivity, eosinophilia and bronchoconstriction elicited by platelet activating factor (PAF). Since PAF may be an important mediator of the exacerbation of bronchial asthma, the inhibition by ketotifen fumarate of PAF-induced effects is consequently of particular interest.

Also of importance, is the effect of ketotifen fumarate on β-adrenergic receptors. Asthma may be associated with a desensitization and a reduced number of β_2-adrenergic receptors.

Pharmacokinetics

Following oral administration of ketotifen fumarate in both man and animals, the absorption is almost complete, as judged from both plasma and urinary excretion levels. The rate of absorption is fast with a half-life of absorption of less than 1 hour. Bioavailability amounts to about 50% due to a first pass effect of 50% in the liver.

After administration of repeated doses the steady state is attained in less than 4 days. This is in accordance with the half-life of elimination recorded for a single dose of ketotifen fumarate.

Distribution studies after oral or intravenous administration in the rat showed a rapid decline in tissue levels of the total radioactivity in parallel with blood concentrations. Liver, kidney and lung had the highest drug levels. No retention was observed in any of the organs as confirmed by the macroautoradiographic studies. The drug passes the maternal/fetal barrier; however, only low levels were found in the fetal tissues. Protein-binding studies in plasma of different species showed that approximately 75% of the drug

was bound within a concentration range of one to two hundred micrograms per mL. Maximal plasma concentrations are reached within 2 to 4 hours.

The metabolism of ketotifen fumarate proceeds by 3 main pathways:

- N-glucuronide formation
- N-demethylation
- reduction of the ketone group of the nucleus in position 10 giving rise to the 10 hydroxyl derivative.

The main metabolite in man found in both urine and plasma is the glucuronide of the unchanged drug. Nor-ketotifen, the N-demethylated metabolite (2% of the dose) and the 10-hydroxyl derivative (less than 1% of the dose) are the only other detectable metabolites present in human urine. Both the 10-OH derivative and N-glucuronide conjugate may reform the intact product by in vivo reversibility. In rats, nor-ketotifen is the main metabolite, while in the rabbit, the main metabolite is the N-sulphate of nor-ketotifen; in the rhesus monkey the metabolic pattern is very complex. The nor-ketotifen metabolite is found to be approximately as active as ketotifen fumarate. Fifteen different metabolites have been isolated and identified in animal and human species and considerable inter-species differences occur.

The excretion of ketotifen fumarate and its metabolites is rapid in both animals and man. More than 60% of the dose of ketotifen fumarate administered is recovered from the urine. This quantity consists mainly of metabolites since only 1% of the dose is found in the urine as the unchanged drug.

Clinical Pharmacology

In a double-blind, placebo-controlled Canadian multicentre 30 week study, the efficacy of Zaditen (ketotifen fumarate) 1 mg b.i.d., was evaluated in 138 asthmatic children aged 5 to 17 years. Over the study period, only the ketotifen fumarate treated patients showed a significant decrease in their daily consumption of theophyllines. Data from periodic spirometric measurements showed from treatment week 6 a significant increase from baseline for FEV_1 and FVC for the ketotifen fumarate patients at many more visits than the increases seen for the placebo-treated patients. Increases in the mean daily peak flow values and decreases in asthma symptoms were found to be statistically significant on more occasions for the ketotifen fumarate than the placebo group. Significantly fewer ketotifen fumarate than placebo patients required hospital visits for asthma and for upper respiratory tract infection (URTI). Patient global evaluation indicated that a significantly higher percentage of ketotifen fumarate (54%) versus placebo (38%) patients reported their asthma to be "absent" to "much improved". Thirty-eight percent (38%) of the placebo patients also reported their asthma to be "unchanged" or "worse", compared with 21% of ketotifen fumarate patients. Clinical evaluation by the physician indicated that the percent of patients with ratings of "good" to "excellent" were significantly higher in the ketotifen fumarate group. Ketotifen fumarate was shown to be well tolerated.

In a double-blind, placebo-controlled European multicenter 12 week study, the efficacy of ketotifen fumarate 0.5-1.0 mg b.i.d. was evaluated in 134 wheezy infants aged between 4 and 50 months. After 12 weeks of treatment, the number of patients with audible wheeze on auscultation fell from 49% to 16% in the ketotifen fumarate group. In the placebo group, there was a minor improvement during the first 4 weeks which was not, however, maintained.

Similarly at 12 weeks, significant improvement in the ketotifen fumarate group occurred in other asthma symptoms including dyspnea, severe and moderate cough, expectoration and nasal discharge and obstruction. More patients were also able to manage with less concomitant medication after 12 weeks of ketotifen fumarate treatment as compared to

placebo. Overall efficacy assessment by the physician was judged to be "very good to good" in 77% of ketotifen fumarate patients compared with 16.5% in placebo patients. However the improvement induced by ketotifen fumarate was slow in onset and did not become significantly different from placebo until after about 10-12 weeks of treatment. Ketotifen fumarate was shown to be well tolerated.

TOXICOLOGY

Acute Toxicity

LD_{50} Values for Zaditen (ketotifen fumarate)

SPECIES	STRAIN	BODY WEIGHT	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	Albino, MF_2	10–31 g	M & F	i.v.	13.8 ± 0
Mouse	Albino, MF_2	10–31 g	M & F	Oral	165 ± 53
Rat	Albino, OFA	155–240 g	M & F	i.v.	5.3 ± 0
Rat	Albino, OFA	155–240 g	M & F	Oral	360 ± 65
Rabbit	Mixed Domestic	2.11–3.09 kg	M & F	i.v.	21.0 ± 5
Rabbit	Mixed Domestic	2.11–3.09 kg	M & F	Oral	790 ± 14

Accelerated and noticeable forced breathing and motor excitation were the first signs of toxicity after the intravenous doses. Whole body cramps, muscular fibrillation, rapid blinking and slit opening of the eyes, coupled with drowsiness appeared later. The surviving animals recovered within hours after administration. After oral administration the type and sequence of signs were similar but slower in onset.

Subacute and Chronic

Rats

In general, toxicity was observed only after long-term administration of ketotifen fumarate at doses which were up to 700 times those required to obtain antiallergic and anti-histaminic effects (see Pharmacology section).

A three-week study in rats at doses of 1, 9 and 83 mg/kg administered in the diet and in doses of 1, 10 and 100 mg/kg administered by gavage showed no mortality. Body weights in the dietary experiment only were decreased during the third week in both sexes at 83 mg/kg, and females at 9 mg/kg. In both studies hepatic lipid was slightly increased and liver weights increased in males only at the highest doses.

A thirteen-week study, at doses of 10, 33 and 157 mg/kg/day given in the diet, resulted in a slightly increased food intake in the lower and mid-dose groups. Slightly increased serum cholesterol levels in these two groups were apparent at week 6 and week 13. Hepatomegaly with some discolouration (brown/yellow) was seen microscopically with 33 and 157 mg/kg/day.

Microscopic adaptive hepatic changes (i.e. occasional hyaline inclusion bodies) were seen at 10 mg/kg/day. With 33 and 157 mg/kg/day, increased hyaline inclusion bodies, cytomegaly and increased stainable fat were noted. Males were more affected than females. Degenerative changes in the beta cells in the pancreatic islets were seen only in males given 157 mg/kg/day. Additional biochemical studies in animals showed higher total lipid values, cholesterol values, higher cytochrome P-450 values, and higher N-demethylase activity at the two higher doses. These observations are consistent with an induction of the mixed function oxidases of the rat combined with slight hepatosteatosis.

In a 98-week (males) or 105-week (females) study of rats receiving 2, 16 and 71 mg/kg/day of ketotifen fumarate in the diet, body weight gain and food consumption were reduced in the high dose animals. There was slight reduction of hemoglobin and

hematocrit mean values from week 26 on in females receiving the high dose. Some degenerative liver changes (liver cell swelling and vacuolization) were seen in the high dose group. There was a slight trend to increased mortality in all dose groups, reaching statistical significance in the high dose females.

Only the high dose males showed slightly elevated SGPT values at weeks 57, 78 and 98, elevated total protein values at weeks 13 and 26, and raised cholesterol values at weeks 13, 26 and 52. After 26 and 52 weeks, males of the treated groups showed distinctly diminished urine volume with significantly raised specific gravity.

Dogs

Dogs were treated with ketotifen fumarate in the diet at doses of 1.25, 5, 20 and 80 mg/kg/day for thirteen weeks, sedation was noted in all dogs in the high dose (80 mg/kg) group and convulsions occurred in one dog. At all dose levels there was a slight increase in food intake and weight gain. With 5 mg/kg/day, SGPT and alkaline phosphatase levels were raised in one out of four dogs. There was no microscopic evidence of hepatotoxicity in these animals. With 20 mg/kg/day, SGPT was slightly raised in two out of four dogs and adaptive microscopic liver changes were observed. Three out of four dogs showed changes in alkaline phosphatase, SGPT, and microscopic evidence at 80 mg/kg. These dogs also showed significant liver weight increase, toxic liver changes and albuminuria. Tachycardia and slight functional ECG changes occurred in the dogs receiving 80 mg/kg/day.

In a 52-week study of dogs receiving ketotifen fumarate at doses of 0.1, 0.5, 5, and 50 mg/kg/day, slight disturbances in equilibrium in two dogs at week 26 and slight clonic-tonic cramps in three dogs occurred at 50 mg/kg. Dogs receiving 0.5 mg/kg or more showed slight increases in food intake and weight gain. One dog in the 5 mg/kg group died in week 30. A slight decrease in mean hemoglobin and hematocrit was found after 3, 6 and 13 weeks in males of the 50 mg/kg group. Significantly decreased urinary potassium excretion and increased serum alkaline phosphatase and SGPT values were also noted in this group. Microscopically, there was hepatocytomegaly with increased

cytoplasmic granularity, increase of pigments in Kupffer cells and slight bile duct proliferation. An increase in minute, dark concrements in the gall bladder was also noted. One dog showed slight ECG changes at 50 mg/kg.

Teratology and Reproductive Studies

No teratogenic or embryolethal activity was seen when ketotifen fumarate was given to female rats in doses of 10, 30, 56 and 100 mg/kg/day between the sixth and fifteenth day of pregnancy. The maternal weight gain and total body weight were decreased at the 56 and 100 mg/kg dose levels. The 100 mg/kg dose was lethal to some of the adult animals. In rabbits, no effect on embryolethal or teratogenic effects were seen following ketotifen fumarate treatment by gavage at daily doses of 5, 15 and 45 mg/kg between the sixth and eighteenth day of pregnancy.

In male rats treated orally for seventy days with 2, 10 and 50 mg/kg of ketotifen fumarate, no adverse effects were observed on fertility or on the development of the offspring up to the dose of 10 mg/kg. In the 50 mg/kg group decreased copulation and fertility index and an increased pre and postnatal mortality of the offspring was seen. However, high mortality occurred in males in the 10 and 50 mg/kg dose groups.

In female rats treated orally with ketotifen fumarate at doses of 2, 10 and 50 mg/kg for two weeks, subsequent mating with untreated males showed no adverse effects either on the fertility of the females or the development of their offspring at any dose level. Impairment of weight gain and increased mortality was seen in mothers treated with 10 and 50 mg/kg.

In female rats treated orally with 2, 10 and 50 mg/kg of ketotifen fumarate from day fifteen postcoitum to day twenty-one post-partum, no adverse effects on the pre- and post-natal development of the offspring were found in the two lower dose groups. However, the 50 mg/kg dose produced mortality in 10 percent of the mothers as well as an increased loss of pups, resulting in slightly decreased litter size and reduced weight gain during the first four days.

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