Erdosteine

Zertin® Oral Preparations

FORMULATION
Erdosteine (Zertin®) 300mg Capsule: With yellow body and green cap, each capsule contains 300mg Erdosteine.

Erdosteine (Zertin®) 175mg/5mL Powder for Suspension: Free flowing white granulate with characteristic pleasant odor and orange flavour. Each 5mL of reconstituted suspension contains 175mg Erdosteine.

INDICATIONS
Treatment of patients with acute and chronic bronchopulmonary diseases, rhinosinusitis, laryngopharyngitis or exacerbations of these chronic diseases in association with mucus production and mucus transport.

DOSAGE & ADMINISTRATION
Adults

300mg Capsule	:	One capsule twice daily.
175mg/5mL Powder for Suspension	:	8.5mL (300mg) twice daily.

No dose adjustment is required in treatment of adult relapses of COPD, or in geriatric patients.

Paediatric use:
As a general rule, 10mg/Kg/day in two administrations at 12 hours intervals.

175mg/5mL Powder for Suspension : the recommended dosage regimen is:

Body Weight (Kg)	Age	Dose
10 – 20 Kg	2 – 6 years	2.5 mL twice daily
21 – 30 Kg	7 – 12 years	5.0 mL twice daily
>30 Kg	> 12 years	5.0 mL three times daily (or 7.5mL twice daily)

Directions for Reconstitution:
To make 60mL reconstituted suspension, loosen the powder by shaking and slowly add 42mL of water, then replace cap and shake well.

To make 100mL reconstituted suspension, loosen the powder by shaking and slowly add 70mL of water, then replace cap and shake well.

Always shake well before use. The reconstituted suspension can be stored in a refrigerator for a maximum of 10 days.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients or to free SH-group containing products.

Hepatic disorders and abnormalities (e.g. increase of serum alkaline phosphatase, transaminases, etc.).

Renal insufficiency (creatinine clearance <25mL/min).

Homocystinuria (the active substance is partially metabolised to homocysteine and there are no data concerning administration of erdosteine in case of congenital errors of the metabolism of aminoacids, especially in those patients obliged to follow a methionine-free dietary regimen).

Phenylketonuria (only for powder for suspension due to the presence of aspartame in this presentation).

WARNINGS & PRECAUTIONS
In case of appearance of classical hypersensitivity signs and symptoms, the treatment with erdosteine must be immediately suspended.

The simultaneous administration of an anti-cough treatment is irrational and could induce the accumulation of liquefied excreatum in the bronchial tree with an increase of risk of superinfection or bronchospasm.

Safety and efficacy in children under two years of age have not been established.

In case of co-treatment with other drugs see the individual product data sheet.

Drug Interaction
No harmful interaction has been observed with other drugs, often used in treatment of respiratory infections and COPD, like theophylline, bronchodilating compounds (corticoid treatment), erythromycin, amoxicillin or co-trimoxazole.

Erdosteine increases amoxicillin concentration in the respiratory tract.

The simultaneous administration of an anti-cough treatment is irrational and could induce the accumulation of liquefied excreatum in the bronchial tree with an increase of risk of superinfection or bronchospasm.

Pregnancy and Lactation
No embryo-foetal abnormalities have been observed in pre-clinical studies.

Information of erdosteine use during pregnancy and nursing is limited. Therefore erdosteine should be administered to pregnant or nursing women only when considered necessary by the clinician.

Effects on the ability to drive and use machines
No effects on the ability to drive and use machines have been observed.

Incompatibilities
None known.

ADVERSE EVENTS
Administration of erdosteine could occasionally cause gastro-intestinal side-effect, like gastric burning, nausea and rarely diarrhea.

In few cases, at the beginning of treatment, ageusia or dysgeusia have been observed.

Hypersensitivity reactions (skin rash, urticaria, unexpected hyperpyrexia) are rare.

The following adverse reaction rates are based on the use of erdosteine in treated population (1520 patients) during phase III clinical trials:

1 to 3%	:	gastralgia, nausea, headache
0.5 to 1%	:	constipation, diarrhea, mouth dryness, vertigo, general malaise.

The observed adverse reactions are not different, from a qualitative point of view, from those observed under placebo.

OVERDOSAGE
No case of overdosage has been reported.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Erdosteine (Zertin®) Capsule and Powder for Suspension contain erdosteine, an original derivative of natural mercapto-aminoacid in thiolactonic form. Following oral administration erdosteine is rapidly metabolised in the liver. The product acts as a pro-drug and its metabolites are mainly responsible for mucolytic activity, due to the presence of free thiol groups which cause the splitting up of the intra- and inter-molecular disulphide bridges of several proteins and mucoproteins present in the expectoration, resulting in a reduction of the mucus elasticity and viscosity.

As a consequence, the reduction of mucus viscosity allows an improved penetration of amoxicillin in the mucus itself, without effects on the amoxicillin specific activity or on the plasmatic levels of amoxicillin and erdosteine. At the same time, the mucociliary transport of mucus improves.

The free thiol groups of erdosteine metabolites inactive oxidizing substances, in particular oxygen radicals, giving erdosteine ability to prevent:

- oxidation of α_1-antitrypsin (which in its reduced form possesses elastase inhibitory activity)
- reduction of the chemotactic activity of polynuclear neutrophils, caused by cigarette smoke
- smoke induced antipyrine oxidation.

Following erdosteine administration, increased plasmatic and bronchoalveolar lavage (BAL) levels of reduced glutathione (GSH) are observed.

Erdosteine has been shown to increase respiratory tract IgA concentration in COPD patients and to prevent the inhibition of granulocytes chemotaxis caused by smoking.

Erdosteine increases the concentration of amoxicillin in the bronchial secretions and co-administration gives a faster response in comparison with mono-therapy with amoxicillin.

The presence of free SH-group in erdosteine metabolites results in reduced bacterial adhesiveness to human mucosal cells, leading to a reduced bacterial virulence.

As in erdosteine, per se, the thiol groups are masked, there are little effects on the GI tract, at recommended dose.

Pharmacokinetics

Erdosteine is rapidly absorbed and metabolised at hepatic level into three main metabolites, containing free SH- groups. The most abundant and active is N-thiodiglycolyl-homocysteine (Metabolite 1, also M1).

After single dose or repeated dose the main pharmacokinetic parameters of erdosteine and its metabolites are not statistically different.

Peak plasma concentrations of Erdosteine (*Zertin*®) and metabolite 1 are achieved in approximately 1 and 3 hours, respectively.

The protein binding rate of erdosteine is about 64.5%.

Elimination occurs mainly by renal route in form of sulphates, only little amount of unmetabolised erdosteine goes through faecal excretion.

Repeated administration and food intake do not affect significantly the pharmacokinetic parameters, as C_{max} and AUC are not affected; after a meal, only T_{max} is slightly shifted.

In particular neither accumulation nor enzymatic induction has been observed.

In case of hepatic impairment an increase of C_{max} and AUC values has been observed. Moreover, in case of severe hepatic dyscrasia an increase of $T1/2\beta$ can be noticed.

In severe renal impairment (creatinine clearance 25 to 40mL/min) there is the risk of metabolites accumulation.

Similar findings result for the 175mg/5mL Powder for Suspension.

PRE-CLINICAL SAFETY DATA

Toxicity

The acute toxicity of erdosteine is low, the LD_{50} values ranging from >5000mg/Kg (p.o.: mouse, rat and i.p. in rat) to >3500mg/Kg (i.v., mouse).

In sub-acute toxicity studies, erdosteine did not cause pathological alterations within the dose range of 100 – 1000mg/Kg/day in rats and of 100mg/Kg/day in dogs (p.o. for 4 weeks), up to 4500mg/Kg/day in rats exposed to aerosol (2 hrs/day) for 4 weeks. Only the highest dose in dogs (400mg/Kg/day) induced a slightly abnormal increase of liver weight with modest histological alterations.

Similarly, during long-term studies (26 weeks) no important toxic symptoms resulted following treatment p.o. with up to 1000mg/Kg/day (rats) and 200mg/Kg/day (dogs, higher dose).

Higher doses in rats induced a reversible decrease of body weight gain and blood protein levels.

No harmful effects on lungs, liver, heart or kidneys were observed.

CNS effects, in terms of sedation, hypothermia and prostration, were observed at extremely high doses (5000mg/Kg p.o., 3500mg/Kg i.v. and i.p. in rats).

The local tolerability was good following oral, inhalation and rectal administration.

Reproductive function

The higher dose (1000mg/Kg/day p.o.) does not appear to induce toxic effects on fertility and general reproductive performance in rats.

Embryo-foetal and perinatal toxicity

Erdosteine up to the daily doses of 1000mg/Kg (rats) and 700mg/Kg (rabbits) by oral route appears as lacking of foetotoxic, embryotoxic and teratogenic effects; the higher dose for rats is also devoid of any effect on the peri- and post-natal parameters.

Mutagenic potential

No mutagenic potential for Erdosteine resulted from studies according to several experimental models: gene mutation on bacteria (Ames test, gene conversion on yeast) and eucaryotes (punctiform mutation); chromosomal aberration in mammals (*in vitro*: Chinese hamster and human lymphocytes; *in vivo* micronucleus test, host mediated assay); host mediated assay and urinary assay were performed as well.

Carcinogenic potential
In view of the molecular structure of the product (a derivative of a natural aminoacid), which does not have any similarity with known carcinogenic compounds, no study was performed.

AVAILABILITY
* *Erdosteine (Zertin®) 300mg Capsule:* Cartons of 20 capsules in blister packs of 10.
** *Erdosteine (Zertin®) 175mg/5mL Powder for Suspension:* Bottles of 60mL and 100mL powder for suspension

STORAGE
Capsule: Store at temperatures not exceeding 25°C. Keep in a dry place.
Powder for Suspension: Store at temperatures not exceeding 30°C. Shake well before use.
The reconstituted suspension can be stored in a refrigerator for a maximum of 10 days.

CAUTION
Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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