SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PETEHA, 250 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Protionamide

One film-coated tablet contains 250 mg protionamide (PTH).

Excipients with known effect: lactose monohydrate (see section 4.4) and Sunset Yellow FCF (E 110) (see section 4.3 and 4.8).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orange, round, biconvex film-coated tablets with a breakline on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of all forms and stages of pulmonary and extrapulmonary tuberculosis as second line drug in the case of proven multidrug resistance of the pathogens against first line drugs

- Treatment of diseases caused by so-called ubiquitous (atypical) mycobacteria

- Treatment of leprosy in the context of modified therapy regimens

PETEHA is always used in combination with other anti-mycobacterial chemotherapeutics and only if susceptibility of the pathogen against protionamide has been proven.

The official guidelines for the proper use of anti-microbial agents need to be taken into account when using PETEHA.

4.2 Posology and method of administration

Protionamide is a second line drug (reserve drug) for the treatment of tuberculosis and of diseases caused by so-called ubiquitous (atypical) mycobacteria. It is always part of a combination therapy with other anti-mycobacterial chemotherapeutics if the susceptibility of the pathogen to protionamide has been proven. The choice of the

therapy regimen is based on the results of the susceptibility test of the specific patient isolate. For the treatment of leprosy, protionamide is used in the context of modified therapy regimens.

Posology

Dosage for tuberculosis and diseases caused by atypical mycobacteria

Adults

Protionamide is dosed according to body weight. Adults are given 15 mg/kg body weight per day.

A maximum daily dose of 1,000 mg should not be exceeded.

The table below shows the number of film-coated tablets for a dosage of 15 mg PTH/kg body weight. The maximum daily dose must not be exceeded.

Body weight	**Daily dose**	
[kg]	**Dose in [mg]**	**Number of PETEHA film-coated tablets**
≤ 25	250	1
25	375	1.5
30	450	2
35	525	2
40	600	2.5
45	675	2.5
50	750	3
55	825	3.5
60	900	3.5
65	975	4
≥ 70	1,000	4

If protionamide is administered in a therapeutic combination with isoniazid, the daily dose of PETEHA needs to be halved. The maximum daily dose then should not exceed 500 mg protionamide (corresponding to 2 film-coated tablets of PETEHA).

Children

Children are given between 7.5 mg and (15) mg PTH/kg body weight per day. The maximum daily dose should not exceed 500 mg protionamide.

Dosage for patients with impaired renal function

Patients with a glomerular filtration rate (GFR) of less than 30 ml/min and dialysis patients are given between 250 mg and 500 mg protionamide (corresponding to 1 to 2 film-coated tablets of PETEHA) per day depending on their body weight. In case of patients with severely impaired renal function, the active substance concentration in the blood needs to be monitored and the dosage may have to be adjusted.

Method of administration

The daily dose of PETEHA is given as single dose during a meal or shortly before going to bed to alleviate the perception of adverse events, in particular of gastrointestinal disorders.

Duration of administration

PETEHA should always be used in combination with other anti-mycobacterial chemotherapeutics. When treating tuberculosis, administration in the initial phase in the context of a triple or quadruple combination therapy and further treatment in the continuation phase with a reduced regimen is advisable.

The duration of the therapy depends on the chemotherapeutic regimen chosen and may vary between 9 months and 2 years.

Dosage for leprosy

To treat leprosy, PETEHA is used in the context of modified therapy regimens in accordance with the dosage recommended in that therapy. The duration of the treatment depends on the therapy regimen chosen.

4.3 Contraindications

PETEHA is contraindicated for

- hypersensitivity to protionamide, to Sunset Yellow FCF (E 110) or to any of the excipients,
- in the case of severe hepatopathy and acute hepatitis,
- in the case of cerebral seizure disorders and psychoses,
- during pregnancy and lactation (see 4.6).

4.4 Special warnings and precautions for use

The hepatotoxicity of protionamide and other potential combination therapy partners used in the therapy regimen chosen make frequent checks of the liver function necessary. The examinations should be carried out before the start of the treatment and at regular intervals thereafter.

In the case of chronic alcohol abuse, the benefits and risks of a protionamide treatment need to be assessed.

Alcohol tolerance is reduced during protionamide treatment. Alcohol should not be consumed during the treatment.

The level of blood sugar of diabetics needs to be monitored frequently. Adjustment of the level of blood sugar may be difficult during a protionamide treatment.

The development of skin reactions, in particular of the mucous membranes, may be an indication of a side effect similar to pellagra which is caused by a lack of nicotinic acid amide and vitamin B. This is to be taken as a warning symptom which usually means that PETEHA treatment is to be discontinued.

Caution is needed in the case of patients with depressions or mental diseases or severe renal impairment (see 4.2).

Caution is also needed in the case of acute gastritis, acute gastric or duodenal ulcers and haemoptysis.

Effects on prothrombin and fibrinogen have been noticed very rarely. Therefore, caution is needed in the case of patients with coagulopathy.

Warning
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

In the context of the therapy regimen for the treatment of tuberculosis, attention must be paid to the additive liver-damaging effects of the individual drugs. This applies in particular to the combination of protionamide and isoniazid, rifampicin, and/or pyrazinamide.

A possible additive liver-damaging effect must also be considered in the case of the combination of protionamide with hormonal contraceptives.

The centrally stimulating/neurotoxic effects are amplified if protionamide and isoniazid and/or psychotropic drugs such as cycloserine or terizidone are given concomitantly. Furthermore, the tolerance of alcohol and medicaments with a centrally attenuating effect may be reduced.

Concomitant intake of alcohol leads to an amplification of the centrally nervous exciting effect.

Protionamide decelerates the degradation of isoniazid and barbiturates.

If protionamide and isoniazid are given concomitantly, then the concentration of protionamide in the blood is raised. Therefore, the protionamide dose should be reduced (see 4.2).

The dose of insulin or peroral blood sugar reducing agents needs to be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy
Thioamides pass the placental barrier. However, there is no sufficient data on the use of protionamide in pregnant women. Experimental studies on animals have shown reproduction toxicity (see 5.3). Since the possibility of a teratogenic effect in humans cannot be ruled out, PETEHA must only be given in case of vital indication.

Breastfeeding
It is not known whether protionamide passes into the breast milk. If treatment during the breastfeeding period is mandatory, the mother should wean her baby.

4.7 Effects on ability to drive and use machines

PETEHA may reduce the ability to react to such a degree that the ability to actively participate in traffic, operate machines or work without safe hold is impaired. Combination with alcohol intensifies this effect.

4.8 Undesirable effects

The undesirable effects of protionamide administration are assessed differently in literature. The frequencies specified here are for orientation only.

Very common: (≥1/10)
Common: (≥ 1/100 to < 1/10)
Uncommon: (≥ 1/1,000 to < 1/100)
Rare: (≥ 1/10,000 to < 1/1,000)
Very rare: (< 1/10,000)
Not known: (cannot be estimated from the available data)

Blood and lymphatic system disorders
Anaemia, methaemoglobinaemia, hypoprothrombinaemia and hypofibrinogenaemia have been reported.

Immune system disorders
Isolated cases: Allergic reactions.

Endocrine disorders
Rare: Gynaecomasty, dysmenorrhoea, amenorrhoea and hypothyroidism.

Metabolism and nutrition disorders
Rare: Fluctuations of blood sugar and reduced levels of blood sugar in diabetics.

Psychiatric disorders
Uncommon: Weak concentration, confusion, psychiatric symptoms such as depressive reactions, excitation, psychoses
Isolated cases: Suicide attempts

Nervous system disorders
Common: Dizziness, headaches
Rare: Convulsive paroxysm, sleep disorders

Damage to the nervus opticus with blurred vision, ocular paralysis and accommodation disorder have been reported.

A shoulder-hand syndrome in the sense of an algodystrophy has also been reported.

In particular with the concomitant administration of isoniazid, impaired vision, polyneuropathies with paraesthesias, amyosthenia and ataxia have been reported.

Eye disorders
Also see nervous system disorders.
Impaired vision including diplopia has been reported.

Ear and labyrinth disorders
Isolated cases: Impairment of the hearing, tinnitus

Respiratory, thoracic and mediastinal disorders
Isolated cases: Haemoptysis

Gastrointestinal disorders
Very common: Taste of metal or sulphur, dry mouth, but also increased salivation, loss of appetite, anorexia, nausea
Uncommon: Vomiting, heartburn, abdominal pain, feeling of fullness, diarrhoea or constipation, meteorism

These undesirable effects vanish quickly and completely if PETEHA® treatment is discontinued.
Slowly increasing dosage may reduce side effects. Reduced dose rates and/or combination with an antiemetic have also proven to be helpful.

Swelling of the parotid has been reported.

Hepatobiliary disorders
Under a therapy with PETEHA, a rise in the transaminase level is *common* which reverses on discontinuation, but *rarely* leads to a manifest liver function disorder with icterus. The hepatotoxicity is critically dependent on previous liver damage (e.g. alcohol disease, post-hepatic liver function disorder) and accumulates in combination with other potentially hepatotoxic drugs (isoniazid, rifampicin, pyrazinamide).

Cases of severe hepatitis with icterus and one case of liver failure have been reported.

Skin and subcutaneous tissue disorders
Pellagroid reactions, photodermatoses, rhagades, stomatitis, acne, cheilitis, glossitis and alopecia have been reported.

Musculoskeletal and connective tissue disorders
Arthralgia, arthritis and amyosthenia have been reported.

Renal and urinary disorders
Urolithiasis has been reported.

Sunset Yellow FCF (E 110) can cause allergic reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

Bundesinstitut für Arzneimittel und Medizinprodukte
(Federal Institute for Drugs and Medical Devices)
Abt. Pharmakovigilanz
(Department of Pharmacovigilance)
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn
website: www.bfarm.de.

4.9 Overdose

There is no experience with overdose.

However, the manifestations of acute overdose could be the undesirable effects specified in section 4.8.
There is no specific treatment for poisoning. No specific antidote is known.
Protionamide is hardly haemodialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
ATC code: J04AD01

Protionamide has an anti-microbial effect which is limited to mycobacteria including *M. tuberculosis* and some so-called atypical mycobacteria. Protionamide has a bacteriostatic effect and a mainly bactericidal effect on proliferative germs.

Mechanism of action
The mechanism of action of ethionamide is understood. Due to the structural similarity of protionamide and ethionamide, it can be assumed that the action of protionamide is also based on the mechanism of action of ethionamide. Ethionamide influences the enoyl-acyl carrier protein reductase component (InhA) of the fatty acid synthase II and leads to an inhibition of the mycolic acid synthesis. This disturbs the bacterium's cell wall synthesis.
Ethionamide is a prodrug which is metabolised into an active metabolite by a specific mycobacterial activator. *In-vivo* studies in mammals and bacteria indicate that the metabolite ethionamide sulphoxide has a biological activity like ethionamide itself. The enzyme responsible for the activation of ethionamide is a flavoprotein monooxygenase (EthA) of the bacterium which oxidises the ethionamide into the matching sulphoxide compound.
Parallel resistances to thiosemicarbazon or thiocarlid are known.
Ethionamid and protionamide are completely cross resistant.

Resistance mechanisms
It is assumed that the resistance mechanisms of ethionamide and the structurally almost identical molecule protionamide are the same. Resistance to ethionamide arises at the molecular level by mutations in the mycobacterium's genome locations which code the enzyme activating the ethionamide (EthA) and/or the enoyl-acyl carrier protein reductase component (InhA) of the fatty acid synthase II.
During monotherapy resistance develops rapidly and after monotherapy over 1 to 3 months a resistance rate of 80-100 % is obtained.

The prevalence of an acquired resistance may vary regionally and in the course of time. Therefore, especially for an adequate treatment of severe infections, regional information on the resistance situation is required.

For the following species an acquired resistance may represent a problem in practice
Mycobacterium tuberculosis
*Mycobacterium bovis**
Mycobacterium kansasii
Mycobacterium malmoense
Mycobacterium xenopi
Naturally resistant species
Mycobacterium avium complex

* naturally intermediary susceptible species

The table above only makes a statement on the probability of whether the micro-organisms are susceptible to PETEHA or not.

In all cases of mycobacterioses an individual susceptibility test has to be carried out for assurance of efficacy of therapy for each patient.

5.2 Pharmacokinetic properties

Absorption
A bioavailability study carried out in 2004 has shown a fast and almost complete (90 %) resorption of protionamide after oral administration. Maximal plasma concentrations (C_{max}) of 811.1 ± 380.6 µg/ml are achieved after intake of 250 mg protionamide. The t_{max} amounts in median to 0.75 h. The AUC 0-t_{last} after intake of 250 mg is 2,186.2 ± 744.2 µg * h/ml.
The bioavailability of thioamides is not impaired by taking with a meal.

Distribution
The concentration of protionamide in healthy and tuberculotic lung tissue is 95 %, i.e. 80 % to 90 % of the concentration in the blood. Protionamide passes well into the liquor. Concentrations comparable with those in blood are achieved.
Protionamide is excreted into the gastric juice and is also found in the sputum.
Protionamide is almost not bound to plasma proteins in the blood. Protionamide sulphoxide, which is also active, is only bound to plasma proteins to a slight extent.

Biotransformation
Protionamide is metabolised into protionamide sulphoxide. Protionamide sulphoxide also has a bactericidal effect.
After a quick distribution into the tissue, the half-life of prothionamide and its metabolite is approximately two hours.

The concomitant administration of protionamide and isoniazid leads to a doubling of the protionamide concentration in the blood. Therefore, the PETEHA® dose is to be halved in a combination therapy with isoniazid.

Elimination
Protionamide and its metabolites are mainly eliminated with the urine. Thioamides are hardly haemodialysable. Pharmacokinetic data on patients with impaired renal function are not available.
Prothonamide and its metabolites have not been found in faeces.

Pharmacokinetic data on children are not available.

5.3 Preclinical safety data

Acute oral toxicity was low in mice, rats and cats. Long-term oral administration of protionamide to rats and dogs was tolerated well.
In-vitro studies on the mutagenic potential of protionamide revealed no signs of a genotoxic potential.
Insufficiently documented studies on carcinogenicity in mice were negative.
Insufficiently documented studies on reproduction toxicity, in which protionamide was orally administered to mice, rats, and rabbits, revealed dose-dependent embryotoxic effects (aborts in mice and rats, elevated resorption rates in rabbits). In rabbits, an additional teratogenicity without any detailed specificity has been mentioned. Studies on fertility as well as on peri-/postnatal development had not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, copovidone, crospovidone (Type A, Ph. Eur.), magnesium stearate (Ph. Eur.) [vegetable], silica colloidal anhydrous, macrogol 6000, hypromellose, microcrystalline cellulose, titanium dioxide (E 171), Sunset Yellow FCF (E 110), lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

Shelf life after opening:
Use the medicinal product within 2 months after first opening of the plastic container. Keep the container tightly closed.

6.4 Special precautions for storage

No particular precautions for storage are necessary for this medicinal product.

Storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

PETEHA film-coated tablets are available in PVC/aluminium blister packs.

PVC/Aluminium blister packs:
Original pack containing 50 film-coated tablets
Original pack containing 100 film-coated tablets
Hospital pack containing 250 film-coated tablets

Plastic container made of polypropylene (PP) with LDPE closure:

Original pack containing 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

Esteve Pharmaceuticals GmbH
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14199 Berlin
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e-mail info.germany@esteve.com

8. MARKETING AUTHORISATION NUMBER

6192821.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 14. June 2005

10. DATE OF REVISION OF THE TEXT

11/2021

11. GENERAL CLASSIFICATION FOR SUPPLY

Prescription-only medicine