ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Wilzin 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 25 mg of zinc (corresponding to 83.92 mg of zinc acetate dihydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Capsule with aqua blue opaque cap and body, imprinted "93-376".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Wilson's disease.

4.2 Posology and method of administration

Wilzin treatment should be initiated under the supervision of a physician experienced in the treatment of Wilson's disease (see section 4.4). Wilzin is a life-long therapy.

There is no difference in dose between symptomatic and presymptomatic patients.
Wilzin is available in hard capsules of 25 mg or 50 mg.

- Adults:
  The usual dose is 50 mg 3 times daily with a maximum dose of 50 mg 5 times daily.
- Children and adolescents:
  Data are very limited in children under 6 years but since the disease is fully penetrant, prophylactic treatment should be considered as early as possible. The recommended dose is as follows:
  - from 1 to 6 years: 25 mg twice daily
  - from 6 to 16 years if bodyweight under 57 kg: 25 mg three times daily
  - from 16 years or if bodyweight above 57 kg: 50 mg three times daily.
- Pregnant women:
  A dose of 25 mg 3 times daily is usually effective but the dose should be adjusted to copper levels (see section 4.4 and section 4.6).

In all cases, dose should be adjusted according to therapeutic monitoring (see section 4.4.).

Wilzin must be taken on an empty stomach, at least 1 hour before or 2-3 hours after meals. In case of gastric intolerance, often occurring with the morning dose, this dose may be delayed to mid-morning, between breakfast and lunch. It is also possible to take Wilzin with a little protein, such as meat (see section 4.5).

In children who are unable to swallow capsules, these should be opened and their content suspended in a little water (possibly sugar or syrup flavoured water).

When switching a patient on chelating treatment to Wilzin for maintenance therapy, the chelating treatment should be maintained and co-administered for 2 to 3 weeks since this is the time it takes for

the zinc treatment to induce maximum metallothionein induction and full blockade of copper absorption. The administration of the chelating treatment and Wilzin should be separated by at least 1 hour.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

Zinc acetate dihydrate is not recommended for the initial therapy of symptomatic patients because of its slow onset of action. Symptomatic patients must be initially treated with a chelating agent; once copper levels are below toxic thresholds and patients are clinically stable, maintenance treatment with Wilzin can be considered.
Nevertheless, while awaiting zinc induced duodenal metallothionein production and consequential effective inhibition of copper absorption, zinc acetate dehydrate could be administered initially in symptomatic patients in combination with a chelating agent.

Although rare, clinical deterioration may occur at the beginning of the treatment, as has also been reported with chelating agents. Whether this is related to mobilisation of copper stores or to natural history of the disease remains unclear. A change of therapy is recommended in this situation.

Caution should be exercised when switching patients with portal hypertension from a chelating agent to Wilzin, when such patients are doing well and the treatment is tolerated. Two patients of a series of 16 died from hepatic decompensation and advanced portal hypertension after being changed from penicillamine to zinc therapy.

Therapeutic monitoring
The aim of the treatment is to maintain the plasma free copper (also known as non-ceruloplasmin plasma copper) below 250 microgram/l (normal: 100-150 microgram/l) and the urinary copper excretion below 125 microgram/24 h (normal: < 50 microgram/24 h). The non-ceruloplasmin plasma copper is calculated by subtracting the ceruloplasmin-bound copper from the total plasma copper, given that each milligram of ceruloplasmin contains 3 micrograms of copper.
The urinary excretion of copper is an accurate reflection of body loading with excess copper only when patients are not on chelation therapy. Urinary copper levels are usually increased with chelation therapy such as penicillamine or trientine.
The level of hepatic copper cannot be used to manage therapy since it does not differentiate between potentially toxic free copper and metallothionein bound copper.
In treated patients, assays of urinary and/or plasma zinc may be a useful measure of treatment compliance. Values of urinary zinc above 2 mg/24 h and of plasma zinc above 1250 microgram/l generally indicate adequate compliance.

Like with all anti-copper agents overtreatment carries the risk of copper deficiency, which is especially harmful for children and pregnant women since copper is required for proper growth and mental development. In these patient groups, urinary copper levels should be kept a little above the upper limit of normal or in the high normal range (i.e. 40 – 50 microgram/24 h).
Laboratory follow-up including haematological surveillance and lipoproteins determination should also be performed in order to detect early manifestations of copper deficiency, such as anaemia and/or leukopenia resulting from bone marrow depression, and decrease in HDL cholesterol and HDL/total cholesterol ratio.
As copper deficiency may also cause myeloneuropathy, physicians should be alert to sensory and motor symptoms and signs which may potentially indicate incipient neuropathy or myelopathy in patients treated with Wilzin.

4.5 Interaction with other medicinal products and other forms of interaction

Other anti-copper agents
Pharmacodynamic studies were conducted in Wilson's disease patients on the combination of Wilzin (50 mg three times daily) with ascorbic acid (1 g once daily), penicillamine (250 mg four times daily), and trientine (250 mg four times daily). They showed no significant overall effect on copper balance although mild interaction of zinc with chelators (penicillamine and trientine) could be detected with decreased faecal but increased urinary copper excretion as compared with zinc alone. This is probably due to some extent of complexion of zinc by the chelator, thus reducing the effect of both active substances.
When switching a patient on chelating treatment to Wilzin for maintenance therapy, the chelating treatment should be maintained and co-administered for 2 to 3 weeks since this is the time it takes for the zinc treatment to induce maximum metallothionein induction and full blockade of copper absorption. The administration of the chelating treatment and Wilzin should be separated by at least 1 hour.

Other medicinal products
The absorption of zinc may be reduced by iron and calcium supplements, tetracyclines and phosphorus-containing compounds, while zinc may reduce the absorption of iron, tetracyclines, fluoroquinolones.

Food
Studies of the co-administration of zinc with food performed in healthy volunteers showed that the absorption of zinc was significantly delayed by many foods (including bread, hard boiled eggs, coffee and milk). Substances in food, especially phytates and fibres, bind zinc and prevent it from entering the intestinal cells. However, protein appears to interfere the least.

4.6 Pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies in patients with Wilson's disease give no indication of harmful effects of zinc on embryo/foetus and mother. Five miscarriages and 2 birth defects (microcephaly and correctable heart defect) were reported in 42 pregnancies.

Animal studies conducted with different zinc salts do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

It is extremely important that pregnant Wilson's disease patients continue their therapy during pregnancy. Which treatment should be used, zinc or chelating agent should be decided by the physician. Dose adjustments to guarantee that the foetus will not become copper deficient must be done and close monitoring of the patient is mandatory (see section 4.4).

Lactation
Zinc is excreted in human breast milk and zinc-induced copper deficiency in the breast-fed baby may occur. Therefore, breast-feeding should be avoided during Wilzin therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Reported adverse reactions are listed below, by system organ class and by frequency.

Frequencies are defined as: 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).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Adverse drug reactions**	
Blood and lymphatic system disorders	*uncommon:*	sideroblastic anaemia, leukopenia
Gastrointestinal disorders	*common:*	gastric irritation
Investigations	*common:*	blood amylase, lipase and alkaline phosphatase increased

Anaemia may be micro-, normo- or macrocytic and is often associated with leukopenia. Bone marrow examination usually reveals characteristic "ringed sideroblasts" (i.e. developing red blood cells containing iron-engorged paranuclear mitochondria). They may be early manifestations of copper deficiency and may recover rapidly following reduction of zinc dosage. However, they must be distinguished from haemolytic anaemia which commonly occurs where there is elevated serum free copper in uncontrolled Wilson's disease.

The most common undesirable effect is gastric irritation. This is usually worst with the first morning dose and disappears after the first days of treatment. Delaying the first dose to mid-morning or taking the dose with a little protein may usually relieve the symptoms.

Elevations of serum alkaline phosphatase, amylase and lipase may occur after a few weeks of treatment, with levels usually returning to high normal within the first one or two years of treatment.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Three cases of acute oral overdose with zinc salts (sulphate or gluconate) have been reported in the literature. Death occurred in a 35 year-old woman on the fifth day after ingestion of 6 g of zinc (40 times the proposed therapeutic dose) and was attributed to renal failure and haemorrhagic pancreatitis with hyperglycaemic coma. The same dose did not produce any symptoms except for vomiting in an adolescent who was treated by whole-bowel irrigation. Another adolescent who ingested 4 g of zinc had serum zinc level of about 50 mg/l 5 hours later and only experienced severe nausea, vomiting and dizziness.

Treatment of overdose should be with gastric lavage or induced emesis as quickly as possible to remove unabsorbed zinc. Heavy metal chelation therapy should be considered if plasma zinc levels are markedly elevated (> 10 mg/l).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: various alimentary tract and metabolism products, ATC code: A16AX05.

Wilson's disease (hepatolenticular degeneration) is an autosomal recessive metabolic defect in hepatic excretion of copper in the bile. Copper accumulation in the liver leads to hepatocellular injury and eventual cirrhosis. When the liver capacity of storing copper is exceeded copper is released into the blood and is taken up in extra hepatic sites, such as the brain, resulting in motor disorders and psychiatric manifestations. Patients may present clinically with predominantly hepatic, neurologic, or psychiatric symptoms.

The active moiety in zinc acetate dihydrate is zinc cation, which blocks the intestinal absorption of copper from the diet and the reabsorption of endogenously secreted copper. Zinc induces the production of metallothionein in the enterocyte, a protein that binds copper thereby preventing its transfer into the blood. The bound copper is then eliminated in the stool following desquamation of the intestinal cells.

Pharmacodynamic investigations of copper metabolism in patients with Wilson's disease included determinations of net copper balance and radiolabelled copper uptake. A daily regimen of 150 mg of Wilzin in three administrations was shown to be effective in significantly reducing copper absorption and inducing a negative copper balance.

5.2 Pharmacokinetic properties

Since the mechanism of action of zinc is an effect on copper uptake at the level of the intestinal cell, pharmacokinetic evaluations based on blood levels of zinc do not provide useful information on zinc bioavailability at the site of action.

Zinc is absorbed in the small intestine and its absorption kinetics suggest a tendency to saturation at increasing doses. Fractional zinc absorption is negatively correlated with zinc intake. It ranges from 30 to 60% with usual dietary intake (7-15 mg/d) and decreases to 7% with pharmacological doses of 100 mg/d.

In the blood, about 80% of absorbed zinc is distributed to erythrocytes, with most of the remainder being bound to albumin and other plasma proteins. The liver is the main storage for zinc and hepatic zinc levels are increased during maintenance therapy with zinc.

The plasma elimination half-life of zinc in healthy subjects is around 1 hour after a dose of 45 mg. The elimination of zinc results primarily from faecal excretion with relatively little from urine and sweat. The faecal excretion is in the greatest part due to the passage of unabsorbed zinc but it is also due to endogenous intestinal secretion.

5.3 Preclinical safety data

Preclinical studies have been conducted with zinc acetate and with other zinc salts. Pharmacological and toxicological data available showed large similarities between zinc salts and among animal species.
The oral LD50 is approximately 300 mg zinc/kg body weight (about 100 to 150 times the human therapeutic dose). Repeat-dose toxicity studies have established that the NOEL (No Observed Effect Level) is about 95 mg zinc/kg body weight (about 48 times the human therapeutic dose).
The weight of evidence, from *in vitro* and *in vivo* tests, suggests that zinc has no clinically relevant genotoxic activity.
Reproduction toxicology studies performed with different zinc salts showed no clinically relevant evidence of embryotoxicity, foetotoxicity or teratogenicity.
No conventional carcinogenicity study has been conducted with zinc acetate dihydrate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
maize starch
magnesium stearate

Capsule shell
gelatin
titanium dioxide (E171)
brilliant blue FCF (E133)

Printing ink
black iron oxide (E172)
shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White HDPE bottle with a polypropylene and HDPE closure and contains a filler (cotton coil). Each bottle contains 250 capsules.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble “Le Wilson”
70, avenue du Général de Gaulle
F-92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/286/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 October 2004

Date of latest renewal: 13 October 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Wilzin 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of zinc (corresponding to 167.84 mg of zinc acetate dihydrate).

Excipients:
Each capsule contains 1.75 mg of sunset yellow FCF (E110)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Capsule with orange opaque cap and body, imprinted "93-377".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Wilson's disease.

4.2 Posology and method of administration

Wilzin treatment should be initiated under the supervision of a physician experienced in the treatment of Wilson's disease (see section 4.4). Wilzin is a life-long therapy.

There is no difference in dose between symptomatic and presymptomatic patients.
Wilzin is available in hard capsules of 25 mg or 50 mg.

- Adults:
  The usual dose is 50 mg 3 times daily with a maximum dose of 50 mg 5 times daily.
- Children and adolescents:
  Data are very limited in children under 6 years but since the disease is fully penetrant, prophylactic treatment should be considered as early as possible. The recommended dosage is as follows:
  - from 1 to 6 years: 25 mg twice daily
  - from 6 to 16 years if bodyweight under 57 kg: 25 mg three times daily
  - from 16 years or if bodyweight above 57 kg: 50 mg three times daily.
- Pregnant women:
  A dose of 25 mg 3 times daily is usually effective but the dose should be adjusted to copper levels (see section 4.4 and section 4.6).

In all cases, dose should be adjusted according to therapeutic monitoring (see section 4.4.).

Wilzin must be taken on an empty stomach, at least 1 hour before or 2-3 hours after meals. In case of gastric intolerance, often occurring with the morning dose, this dose may be delayed to mid-morning, between breakfast and lunch. It is also possible to take Wilzin with a little protein, such as meat (see section 4.5).

In children who are unable to swallow capsules, these should be opened and their content suspended in a little water (possibly sugar or syrup flavoured water).

When switching a patient on chelating treatment to Wilzin for maintenance therapy, the chelating treatment should be maintained and co-administered for 2 to 3 weeks since this is the time it takes for the zinc treatment to induce maximum metallothionein induction and full blockade of copper absorption. The administration of the chelating treatment and Wilzin should be separated by at least 1 hour.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

Zinc acetate dihydrate is not recommended for the initial therapy of symptomatic patients because of its slow onset of action. Symptomatic patients must be initially treated with a chelating agent; once copper levels are below toxic thresholds and patients are clinically stable, maintenance treatment with Wilzin can be considered.
Nevertheless, while awaiting zinc induced duodenal metallothionein production and consequential effective inhibition of copper absorption, zinc acetate dehydrate could be administered initially in symptomatic patients in combination with a chelating agent.

Although rare, clinical deterioration may occur at the beginning of the treatment, as has also been reported with chelating agents. Whether this is related to mobilisation of copper stores or to natural history of the disease remains unclear. A change of therapy is recommended in this situation.

Caution should be exercised when switching patients with portal hypertension from a chelating agent to Wilzin, when such patients are doing well and the treatment is tolerated. Two patients of a series of 16 died from hepatic decompensation and advanced portal hypertension after being changed from penicillamine to zinc therapy.

Therapeutic monitoring
The aim of the treatment is to maintain the plasma free copper (also known as non-ceruloplasmin plasma copper) below 250 microgram/l (normal: 100-150 microgram/l) and the urinary copper excretion below 125 microgram/24 h (normal: < 50 microgram/24 h). The non-ceruloplasmin plasma copper is calculated by subtracting the ceruloplasmin-bound copper from the total plasma copper, given that each milligram of ceruloplasmin contains 3 micrograms of copper.
The urinary excretion of copper is an accurate reflection of body loading with excess copper only when patients are not on chelation therapy. Urinary copper levels are usually increased with chelation therapy such as penicillamine or trientine.
The level of hepatic copper cannot be used to manage therapy since it does not differentiate between potentially toxic free copper and metallothionein bound copper.
In treated patients, assays of urinary and/or plasma zinc may be a useful measure of treatment compliance. Values of urinary zinc above 2 mg/24 h and of plasma zinc above 1250 microgram/l generally indicate adequate compliance.

Like with all anti-copper agents overtreatment carries the risk of copper deficiency, which is especially harmful for children and pregnant women since copper is required for proper growth and mental development. In these patient groups, urinary copper levels should be kept a little above the upper limit of normal or in the high normal range (i.e. 40 – 50 microgram/24 h).
Laboratory follow-up including haematological surveillance and lipoproteins determination should also be performed in order to detect early manifestations of copper deficiency, such as anaemia and/or leukopenia resulting from bone marrow depression, and decrease in HDL cholesterol and HDL/total cholesterol ratio.
As copper deficiency may also cause myeloneuropathy, physicians should be alert to sensory and motor symptoms and signs which may potentially indicate incipient neuropathy or myelopathy in patients treated with Wilzin.

The capsule shell contains sunset yellow FCF (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Other anti-copper agents
Pharmacodynamic studies were conducted in Wilson's disease patients on the combination of Wilzin (50 mg three times daily) with ascorbic acid (1 g once daily), penicillamine (250 mg four times daily), and trientine (250 mg four times daily). They showed no significant overall effect on copper balance although mild interaction of zinc with chelators (penicillamine and trientine) could be detected with decreased faecal but increased urinary copper excretion as compared with zinc alone. This is probably due to some extent of complexion of zinc by the chelator, thus reducing the effect of both active substances.
When switching a patient on chelating treatment to Wilzin for maintenance therapy, the chelating treatment should be maintained and co-administered for 2 to 3 weeks since this is the time it takes for the zinc treatment to induce maximum metallothionein induction and full blockade of copper absorption. The administration of the chelating treatment and Wilzin should be separated by at least 1 hour.

Other medicinal products
The absorption of zinc may be reduced by iron and calcium supplements, tetracyclines and phosphorus-containing compounds, while zinc may reduce the absorption of iron, tetracyclines, fluoroquinolones.

Food
Studies of the co-administration of zinc with food performed in healthy volunteers showed that the absorption of zinc was significantly delayed by many foods (including bread, hard boiled eggs, coffee and milk). Substances in food, especially phytates and fibres, bind zinc and prevent it from entering the intestinal cells. However, protein appears to interfere the least.

4.6 Pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies in patients with Wilson's disease give no indication of harmful effects of zinc on embryo/foetus and mother. Five miscarriages and 2 birth defects (microcephaly and correctable heart defect) were reported in 42 pregnancies.

Animal studies conducted with different zinc salts do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

It is extremely important that pregnant Wilson's disease patients continue their therapy during pregnancy. Which treatment should be used, zinc or chelating agent should be decided by the physician. Dose adjustments to guarantee that the foetus will not become copper deficient must be done and close monitoring of the patient is mandatory (see section 4.4).

Lactation
Zinc is excreted in human breast milk and zinc-induced copper deficiency in the breast-fed baby may occur. Therefore, breast-feeding should be avoided during Wilzin therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Reported adverse reactions are listed below, by system organ class and by frequency.

Frequencies are defined as: 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).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Adverse drug reactions**	
Blood and lymphatic system disorders	*uncommon:*	sideroblastic anaemia, leukopenia
Gastrointestinal disorders	*common:*	gastric irritation
Investigations	*common:*	blood amylase, lipase and alkaline phosphatase increased

Anaemia may be micro-, normo- or macrocytic and is often associated with leukopenia. Bone marrow examination usually reveals characteristic "ringed sideroblasts" (i.e. developing red blood cells containing iron-engorged paranuclear mitochondria). They may be early manifestations of copper deficiency and may recover rapidly following reduction of zinc dosage. However, they must be distinguished from haemolytic anaemia which commonly occurs where there is elevated serum free copper in uncontrolled Wilson's disease.

The most common undesirable effect is gastric irritation. This is usually worst with the first morning dose and disappears after the first days of treatment. Delaying the first dose to mid-morning or taking the dose with a little protein may usually relieve the symptoms.

Elevations of serum alkaline phosphatase, amylase and lipase may occur after a few weeks of treatment, with levels usually returning to high normal within the first one or two years of treatment.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Three cases of acute oral overdose with zinc salts (sulphate or gluconate) have been reported in the literature. Death occurred in a 35 year-old woman on the fifth day after ingestion of 6 g of zinc (40 times the proposed therapeutic dose) and was attributed to renal failure and haemorrhagic pancreatitis with hyperglycaemic coma. The same dose did not produce any symptoms except for vomiting in an adolescent who was treated by whole-bowel irrigation. Another adolescent who ingested 4 g of zinc had serum zinc level of about 50 mg/l 5 hours later and only experienced severe nausea, vomiting and dizziness.

Treatment of overdose should be with gastric lavage or induced emesis as quickly as possible to remove unabsorbed zinc. Heavy metal chelation therapy should be considered if plasma zinc levels are markedly elevated (> 10 mg/l).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: various alimentary tract and metabolism products, ATC code: A16AX05.

Wilson's disease (hepatolenticular degeneration) is an autosomal recessive metabolic defect in hepatic excretion of copper in the bile. Copper accumulation in the liver leads to hepatocellular injury and eventual cirrhosis. When the liver capacity of storing copper is exceeded copper is released into the blood and is taken up in extra hepatic sites, such as the brain, resulting in motor disorders and psychiatric manifestations. Patients may present clinically with predominantly hepatic, neurologic, or psychiatric symptoms.

The active moiety in zinc acetate dihydrate is zinc cation, which blocks the intestinal absorption of copper from the diet and the reabsorption of endogenously secreted copper. Zinc induces the production of metallothionein in the enterocyte, a protein that binds copper thereby preventing its transfer into the blood. The bound copper is then eliminated in the stool following desquamation of the intestinal cells.

Pharmacodynamic investigations of copper metabolism in patients with Wilson's disease included determinations of net copper balance and radiolabelled copper uptake. A daily regimen of 150 mg of Wilzin in three administrations was shown to be effective in significantly reducing copper absorption and inducing a negative copper balance.

5.2 Pharmacokinetic properties

Since the mechanism of action of zinc is an effect on copper uptake at the level of the intestinal cell, pharmacokinetic evaluations based on blood levels of zinc do not provide useful information on zinc bioavailability at the site of action.

Zinc is absorbed in the small intestine and its absorption kinetics suggest a tendency to saturation at increasing doses. Fractional zinc absorption is negatively correlated with zinc intake. It ranges from 30 to 60% with usual dietary intake (7-15 mg/d) and decreases to 7% with pharmacological doses of 100 mg/d.

In the blood, about 80% of absorbed zinc is distributed to erythrocytes, with most of the remainder being bound to albumin and other plasma proteins. The liver is the main storage for zinc and hepatic zinc levels are increased during maintenance therapy with zinc.

The plasma elimination half-life of zinc in healthy subjects is around 1 hour after a dose of 45 mg. The elimination of zinc results primarily from faecal excretion with relatively little from urine and sweat. The faecal excretion is in the greatest part due to the passage of unabsorbed zinc but it is also due to endogenous intestinal secretion.

5.3 Preclinical safety data

Preclinical studies have been conducted with zinc acetate and with other zinc salts. Pharmacological and toxicological data available showed large similarities between zinc salts and among animal species.
The oral LD50 is approximately 300 mg zinc/kg body weight (about 100 to 150 times the human therapeutic dose). Repeat-dose toxicity studies have established that the NOEL (No Observed Effect Level) is about 95 mg zinc/kg body weight (about 48 times the human therapeutic dose).
The weight of evidence, from *in vitro* and *in vivo* tests, suggests that zinc has no clinically relevant genotoxic activity.
Reproduction toxicology studies performed with different zinc salts showed no clinically relevant evidence of embryotoxicity, foetotoxicity or teratogenicity.
No conventional carcinogenicity study has been conducted with zinc acetate dihydrate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

maize starch
magnesium stearate

Capsule shell
gelatin
titanium dioxide (E171)
sunset yellow FCF (E110)

Printing ink
black iron oxide (E172)
shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White HDPE bottle with a polypropylene and HDPE closure and contains a filler (cotton coil). Each bottle contains 250 capsules.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble “Le Wilson”
70, avenue du Général de Gaulle
F-92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/286/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 October 2004
Date of latest renewal: 13 October 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Recordati Rare Diseases
Immeuble "Le Wilson"
70, avenue du Général de Gaulle
F-92800 Puteaux
France

or

Recordati Rare Diseases
Eco River Parc
30, rue des Peupliers
F-92000 Nanterre
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

OUTER CARTON BOX AND BOTTLE LABEL (Wilzin 25 mg hard capsules)

1. NAME OF THE MEDICINAL PRODUCT

Wilzin 25 mg hard capsules
Zinc

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 25 mg of zinc (corresponding to 83.92 mg of zinc acetate dihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble “Le Wilson”
70, avenue du Général de Gaulle
F-92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/286/001

13. MANUFACTURER’S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION ON BRAILLE

Wilzin 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

OUTER CARTON BOX AND BOTTLE LABEL (Wilzin 50 mg hard capsules)

1. NAME OF THE MEDICINAL PRODUCT

Wilzin 50 mg hard capsules
Zinc

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of zinc (corresponding to 167.84 mg of zinc acetate dihydrate) .

3. LIST OF EXCIPIENTS

Contains E110. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble “Le Wilson”
70, avenue du Général de Gaulle
F-92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/286/002

13. MANUFACTURER’S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION ON BRAILLE

Wilzin 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

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B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Wilzin 25 mg hard capsules
Wilzin 50 mg hard capsules
zinc

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT WILZIN IS AND WHAT IT IS USED FOR

Wilzin belongs to a group of medicines called Various Alimentary Tract and metabolism products.

Wilzin is indicated in the treatment of Wilson's disease, which is a rare inherited defect in copper excretion. Dietary copper, which cannot be properly eliminated, accumulates first in the liver, then in other organs such as the eyes and the brain. This potentially leads to liver damage and neurological disorders.
Wilzin blocks the absorption of copper from the intestine thereby preventing its transfer into the blood and its further accumulation in the body. Unabsorbed copper is then eliminated in the stool.

Wilson's disease will persist during the entire lifetime of the patient and therefore the need for this treatment is life-long.

2. BEFORE YOU TAKE WILZIN

Do not take Wilzin
If you are allergic (hypersensitive) to zinc or any of the other ingredients of Wilzin.

Take special care with Wilzin
Wilzin is usually not recommended for initial therapy of patients with signs and symptoms of Wilson's disease because of its slow onset of action.

If you are currently treated with another anti-copper agent, for example, penicillamine, your doctor may add Wilzin before stopping the initial treatment.

As with other anti-copper agents such as penicillamine, your symptoms may get worse after starting the treatment. In this case, you must inform your doctor.

In order to follow up your condition and treatment your doctor will check your blood and urine on a regular basis. This is to ensure that you receive sufficient treatment. Monitoring may detect evidence

of insufficient treatment (copper excess) or excessive treatment (copper deficiency), both of which can be harmful, particularly to growing children and pregnant women.
You should tell your doctor if you experience unusual muscle weakness or abnormal feeling in your limbs as this may indicate excessive treatment.

Taking other medicines
Please tell your doctor or your pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Please consult your doctor before taking any other medicines which may reduce the effectiveness of Wilzin, such as iron, calcium supplements, tetracyclines (antibiotics) or phosphorus. Conversely, the effectiveness of some medicines, such as iron, tetracyclines or fluoroquinolones (antibiotics), may be reduced by Wilzin.

Taking Wilzin with food and drink
Wilzin should be taken on an empty stomach, separated from mealtimes. Dietary fibres and some dairy products, in particular, delay the absorption of zinc salts. Some patients experience stomach upset after the morning dose. Please discuss the matter with your Wilson's disease doctor if this affects you. This side effect may be reduced by postponing the first dose of the day until mid-morning (between breakfast and the midday meal). It may also be minimised by taking the first dose of Wilzin with a small amount of protein-containing food, such as meat (but not milk).

Pregnancy
Please consult your doctor if you plan to become pregnant. It is very important to continue anti-copper therapy during pregnancy.
If you become pregnant during therapy with Wilzin, your doctor will decide which treatment and which dose is best in your situation.

Breast-feeding
Breast-feeding should be avoided if you are on Wilzin therapy. Please discuss with your doctor.

Driving and using machines
No studies of the effects on the ability to drive and use machines have been performed.

Important information about some of the ingredients of Wilzin
Wilzin 50 mg hard capsules contains sunset yellow FCF (E110) which may cause allergic reactions.

3. HOW TO TAKE WILZIN

Always take Wilzin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. For the different dose regimens Wilzin is available in hard capsules of 25 mg or 50 mg.

- *For adults*:
  The usual dose is 1 hard capsule of Wilzin 50 mg (or 2 hard capsules of Wilzin 25 mg) three times daily with a maximum dose of 1 hard capsule of Wilzin 50 mg (or 2 hard capsules of Wilzin 25 mg) five times daily.
- *For children and adolescents:*
  The usual dose is:
  - from 1 to 6 years: 1 hard capsule of Wilzin 25 mg twice daily
  - from 6 to 16 years if bodyweight under 57 kg: 1 hard capsule of Wilzin 25 mg three times daily
  - from 16 years or if bodyweight above 57 kg: 2 hard capsules of Wilzin 25 mg or 1 hard capsule of Wilzin 50 mg three times daily.

Always take Wilzin on an empty stomach, at least one hour before or 2-3 hours after meals.

If the morning dose is not well tolerated (see section 4) it is possible to delay it to mid-morning, between breakfast and lunch. It is also possible to take Wilzin with a little protein, such as meat.

If you have been prescribed Wilzin with another anti-copper agent, such as penicillamine, keep an interval of at least 1 hour between the two medicines.

To administer Wilzin to children who are unable to swallow capsules, open the capsule and mix the powder with a little water (possibly flavoured with sugar or syrup).

If you take more Wilzin than you should:
If you take more Wilzin than prescribed, you may experience nausea, vomiting and dizziness. In this case you must ask your doctor for advice.

If you forget to take Wilzin:
Do not take a double dose to make up for a forgotten individual dose.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Wilzin can cause side effects, although not everybody gets them..

These side effects may occur with certain frequencies, which are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Common:

- After Wilzin intake, gastric irritation may occur, especially at the beginning of treatment.
- Changes in blood tests have been reported, including an increase in some liver and pancreatic enzymes.

Uncommon:

- A decrease in blood red and white cells may occur.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE WILZIN

- Keep out of the reach and sight of children.

- Do not use Wilzin after the expiry date stated on the bottle and the carton, after EXP. The expiry date refers to the last day of that month.

- Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Wilzin contains

The active substance is zinc. Each hard capsule contains 25 mg of zinc (corresponding to 83.92 mg of zinc acetate dihydrate) or 50 mg of zinc (corresponding to 167.84 mg of zinc acetate dihydrate).
The other ingredients are maize starch and magnesium stearate. The capsule shell contains gelatin, titanium dioxide (E171) and either brilliant blue FCF (E133) for Wilzin 25 mg, or sunset yellow FCF (E110) for Wilzin 50 mg. The printing ink contains black iron oxide (E172) and shellac.

What Wilzin looks like and contents of the pack

Wilzin 25 mg is an aqua blue hard capsule imprinted "93-376".
Wilzin 50 mg is an orange opaque hard capsule imprinted "93-377".
It is available in packs of 250 hard capsules in a polyethylene bottle closed by a polypropylene and polyethylene closure. The bottle also contains a cotton filler.

Marketing Authorisation Holder
Recordati Rare Diseases
Immeuble "Le Wilson"
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F-92800 Puteaux
France

Manufacturer
Recordati Rare Diseases
Immeuble "Le Wilson"
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F-92800 Puteaux
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or

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.