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## TRANSPARENCY COMMITTEE

Opinion  
23 July 2014

### TROLOVOL 300 mg, film-coated tablet

B/30 (CIP: 34009 320 316 9 6)

Applicant: IMAXO

INN	D-penicillamine
ATC Code (2012)	M01CC01 (Specific antirheumatic agents)
Reason for the review	<b>Renewal of inclusion</b>
List concerned	<b>National Health Insurance (French Social Security Code L.162-17)</b>
Indications concerned	<b>"Disease-modifying treatment of rheumatoid arthritis Treatment of Wilson's disease."</b>

## 01 ADMINISTRATIVE AND REGULATORY INFORMATION

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Marketing Authorisation (national)	Initial date (national): 6 September 1976 validated on 17 February 1998
Prescribing and dispensing conditions/special status	List I

ATC Classification	2012 M Musculo-skeletal system M01 Antiinflammatory and antirheumatic products M01C Specific antirheumatic agents M01CC Penicillamine and similar agents M01CC01 Penicillamine
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## 02 BACKGROUND

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Review of the proprietary medicinal product included again on the list of medicines refundable by National Health Insurance for a period of 5 years starting on 31/12/2005 (Official Gazette of 28/04/2006).

During the last review of the proprietary medicinal product dated 30 November 2005, the Transparency Committee awarded a significant AB in all MA indications.

## 03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

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### 03.1 Therapeutic indications

"Disease-modifying treatment of rheumatoid arthritis  
Treatment of Wilson's disease"

### 03.2 Dosage

#### Rheumatoid arthritis:

The dosage should be gradually increased to reach the minimal effective dose, without exceeding it:

- 300 mg per day, the first month,
- 600 mg per day, the second month.

If therapeutic effects occur at this dose, it is not necessary to increase it, otherwise go to 900 mg per day. Whenever possible, avoid exceeding 900 mg per day.

Always determine the minimal effective dose.

The tablets must be taken on an empty stomach (between meals).

#### **Wilson's disease:**

- Adults:

1200 to 1800 mg per day in several divided doses, 30 minutes prior to a meal. This dose should be gradually reached in order to reduce hypersensitivity reactions.

After stabilisation of the disease, reduce the dosage to a daily dose of 600 mg to 900 mg. Then, maintain the lowest effective dose needed to obtain a negative copper balance. A dose of 1800 mg per day should not be maintained for more than a year.

- Children:

Up to 20 mg/kg/day in several divided doses prior to a meal. The minimum daily dose is 500 mg.

## **04 ANALYSIS OF NEW AVAILABLE DATA**

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### **04.1 Efficacy**

#### **4.1.1 Rheumatoid arthritis**

The company has not provided any new efficacy data.

The literature search conducted by the HAS documentation department could not identify clinical data with acceptable methodology published since the Committee's last opinion to assess the efficacy of D-penicillamine in the treatment of rheumatoid arthritis.

Its structural efficacy in rheumatoid arthritis has not been demonstrated.

#### **4.1.2 Wilson's disease**

The company provided three publications<sup>1,2,3</sup> on the efficacy of penicillamine for this indication.

A literature review included studies published before January 2008, concerning the effectiveness of copper chelating agents and zinc in monotherapy (Wiggelinkhuizen et al. 2009). This review is comprised of a randomised study and 12 observational studies. These studies were heterogeneous and their methodological quality was poor. Eleven studies were uncontrolled: 7 with penicillamine only, 4 with zinc only. Two studies, only one of which was a controlled, randomised study, compared D-penicillamine and zinc.

One retrospective study included 24 patients treated with penicillamine for  $15 \pm 12$  years between 1969 and 2009 (Lowette 2010). Diagnosed at the age of 21 (8-40) on average, the majority of patients (67%) had liver symptoms, 5 (21%) had neurological symptoms and 3 (12%) were asymptomatic.

The objective of one study was to measure copper and zinc levels in the serum, urine and hair of patients treated with 900 mg/d of D-penicillamine (n = 8), 100 mg/d of zinc (n = 8) or both combined (n = 8) for 2 to 15 years (Dastych, 2010).

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<sup>1</sup> Wiggelinkhuizen M et al. Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson disease. *Aliment Pharmacol. Ther.* 2009; 29: 947-958

<sup>2</sup> Lowette KF et al. Wilson's disease: long-term follow-up of a cohort of 24 patients treated with D-penicillamine. *Eur. J. Gastroenterol. Hepatol.* 2010; 22: 564-571

<sup>3</sup> Dastych M et al. Copper and zinc in the serum, urine, and hair of patients with Wilson's disease treated with penicillamine and zinc. *Biol. Trace Elem. Res.* 2010; 133: 265-269

These publications do not change the role of D-penicillamine in the therapeutic management of Wilson's disease.

## 04.2 Safety/Adverse effects

► The company has provided new safety data from pharmacovigilance reports covering the periods from 01/04/2001 to 30/11/2010. Twenty-three cases were reported in total, including 9 unexpected cases (cognitive impairment, paraesthesia in the leg, dyspnoea, hepatitis, pancreatitis (2 cases), hyperthermia, delusions, leg ulcer healing problem).

► No change has been made to the SPC since the Committee's previous opinion dated 30 November 2005.

► These data confirm the mediocre known safety profile of D-penicillamine.

## 04.3 Usage/prescription data

According to IMS data (winter 2013 moving annual total), TROLOVOL was prescribed 1541 times; this small number of prescriptions cannot be used to reliably analyse the data.

According to GERS [Group for the Collection and Compilation of Statistics] data, sales of TROLOVOL have been decreasing since the 2000s (from 50,479 boxes in 2005 to 33,040 boxes in 2010): 27,941 boxes of TROLOVOL were sold in pharmacy between April 2012 and March 2013 and 26,991 boxes were sold between April 2013 and March 2014.

We do not have specific use data for RA.

## 04.4 Therapeutic strategy

### 4.4.1 Rheumatoid arthritis

The current therapeutic management of rheumatoid arthritis involves the prescription of an immediate action anti-inflammatory drug (NSAID, corticosteroids) and a disease-modifying drug in order to induce clinical and biochemical remission. Methotrexate is the classic reference disease-modifying drug for rheumatoid arthritis. In the event of an inadequate response or contraindication to methotrexate, the following can be used depending on the clinical-biological presentation of the disease and the pathophysiological predisposition of the patient:

- another classic disease-modifying treatment as monotherapy or;
- a combination of classic disease-modifying treatments or;
- an anti-TNF.

#### Role of D-penicillamine in the therapeutic strategy:

In the absence of current national guidelines for the therapeutic management of rheumatoid arthritis, the European EULAR recommendations<sup>4</sup> (European League Against Rheumatism) were taken into account.

D-penicillamine was excluded from the earlier draft of the 2012 EULAR recommendations as the efficacy data were deemed to be inadequate. It is also not included in the current version of the 2013 EULAR recommendations.

The French Society of Rheumatology (SFR) was asked by the Transparency Committee office for a decision on the role of non-biological disease-modifying treatments in the treatment of RA. This scholarly society judged that D-penicillamine has no role in the therapeutic management of RA and is no longer prescribed by French rheumatologists.

It should be noted that the 2012 recommendations of the American College of Rheumatology (ACR)<sup>5</sup> do not cite it either.

In view of these elements, the Transparency Committee considers that the role of D-penicillamine (TROLOVOL) in the therapeutic strategy for rheumatoid arthritis has changed since the last renewal of inclusion by the Commission on 30 November 2005: **it no longer has a role in the therapeutic strategy for RA compared with the available alternatives.**

#### **4.4.2 Wilson's disease**

In Wilson's disease, the goal of treatment is to reduce the accumulation of copper and therefore its hepatic and neurological toxicity. The choice of treatment is influenced by the clinical presentation, stage of the disease and the patient's tolerance to D-penicillamine, which is not as well tolerated as zinc. Due to its slow onset, zinc acetate dihydrate is not recommended as the initial therapy for symptomatic patients. These patient must first be given a chelating agent (TROLOVOL). A maintenance treatment with WILZIN (zinc acetate dihydrate) can only be considered when the copper concentrations are below the toxic threshold and the patients are clinically stabilised. However, the initial administration of zinc acetate dihydrate, combined with a chelating agent, is possible in symptomatic patients. Consequently, TROLOVOL is a first-line treatment for Wilson's disease.

Since the last renewal of inclusion by the Commission on 30 November 2005, the role of TROLOVOL in the therapeutic strategy for Wilson's disease has not been changed.

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<sup>4</sup> Smolen et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann. Rheum. Dis.* 2014; 73: 492-509.

<sup>5</sup> Singh et al. 2012. Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. *Arthritis Care & Research* 2012; 64: 625–639

## 05 TRANSPARENCY COMMITTEE CONCLUSIONS

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In view of all the above information, and following the debate and vote, the Committee believes that the conclusions of its previous opinion of 30 November 2005 have been modified as follows:

### 05.1 Actual Benefit:

#### 5.1.1 Disease-modifying treatment of rheumatoid arthritis

- ▶ Rheumatoid arthritis is a serious and disabling chronic disease.
- ▶ TROLOVOL is intended as symptomatic therapy.
- ▶ Its efficacy/adverse effects ratio is modest.
- ▶ There are treatment alternatives (disease-modifying non-biological treatments and biotherapies).
- ▶ TROLOVOL no longer has a role in the disease-modifying treatment of rheumatoid arthritis compared with the available alternatives.

**Taking account of these points, the Committee considers that the actual benefit of D-penicillamine (TROLOVOL) is insufficient compared with the available alternatives to justify reimbursement by the National Health Insurance in the indication of disease-modifying treatment of rheumatoid arthritis.**

#### 5.1.2 Treatment of Wilson's disease

- ▶ Wilson's disease (hepatolenticular degeneration) is an autosomal recessive familial disease, characterised by the accumulation of copper first in the liver, then in the brain and other tissues. Patients with this disease predominantly have liver, neurological and psychiatric clinical symptoms.
- ▶ TROLOVOL is intended as curative therapy.
- ▶ Its efficacy/adverse effects ratio is still high.
- ▶ There are few therapeutic alternatives:
  - WILZIN, capsule (zinc acetate dihydrate)
  - TRIENTINE, capsule (trientine dihydrochloride) under a limited ATU [Temporary authorisation for use] status in the event of failure, intolerance or contraindication to D-penicillamine.
- ▶ TROLOVOL is a first-line therapy.

**The Committee considers that the actual benefit of TROLOVOL remains substantial in the indication treatment of Wilson's disease.**

## 05.2 Transparency Committee recommendations:

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance for Wilson's disease but does not recommend this in the indication "disease-modifying treatment of rheumatoid arthritis".

▶ **Proposed reimbursement rate: 65% (only for Wilson's disease)**

▶ **Packaging**

Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.