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TRANSPARENCY COMMITTEE

Opinion
23 July 2014

ALLOCHRYSSINE 25 mg, solution for IM injection

1 × 2 ml ampoule + 1 × 8 ml ampoule of diluent (CIP: 34009 300 279 0 5)

ALLOCHRYSSINE 50 mg, solution for IM injection

1 × 2 ml ampoule + 1 × 8 ml ampoule of diluent (CIP: 34009 300 280 9 4)

ALLOCHRYSSINE 100 mg, solution for IM injection

1 × 2 ml ampoule + 1 × 8 ml ampoule of diluent (CIP: 34009 300 281 5 5)

Applicant: PRIMIUS LAB LIMITED

INN	Sodium aurothiopropanolsulfonate
ATC Code (2012)	M01CB05 (Gold preparations)
Reason for the review	Renewal of inclusion
List concerned	National Health Insurance (French Social Security Code L.162-17)
Indication concerned	“Long-acting symptomatic treatment of chronic inflammatory rheumatic diseases, in particular rheumatoid arthritis.”

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (national procedure)	Initial date: 17 June 1976 validated on 19 January 1998
Prescribing and dispensing conditions /special status	List I

ATC Classification	2012 M M01 M01C M01CB M01CB05	Musculo-skeletal system Antiinflammatory and antirheumatic products Specific antirheumatic agents Gold preparations aurotioprol
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02 BACKGROUND

Review of the ALLOCHRYSSINE proprietary medicinal products, the inclusion of which on the list of proprietary medicinal products reimbursed by National Health Insurance was renewed for a 5-year period commencing on 31.12.2005 (opinion published in the Official Gazette of 23.12.2008).

When inclusion was last renewed on 29 March 2006, the Committee classified the AB of this proprietary medicinal product as substantial.

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications

“Long-acting symptomatic treatment of chronic inflammatory rheumatic diseases, in particular rheumatoid arthritis.”

03.2 Dosage

“Adults:

Treatment should be commenced with weekly injections of 25 mg, followed thereafter by weekly injections of 50 to 100 mg up to a total dose of 1.2 to 1.5 g.

Maintenance therapy as a monthly injection of 50 to 100 mg for as long as the patient is able to tolerate it.

Children:

Treatment should be commenced with 0.25 mg/kg in the first week, 0.5 mg/kg in the second week, thereafter 1 mg/kg not exceeding a maximum weekly dose of 50 mg.”

04 ANALYSIS OF NEW AVAILABLE DATA

04.1 Efficacy

The applicant has not supplied any relevant new clinical data evaluating the efficacy of gold salts in RA published since the last Committee opinion in 2006.

The literature search carried out by the documentation department of HAS did not identify clinical data with acceptable methodology published since the last Committee opinion and enabling the efficacy of aurotioprol in the treatment of rheumatoid arthritis to be assessed.

04.2 Safety/Adverse effects

▶ The applicant has supplied safety data from the available periodic pharmacovigilance reports (PSURs) covering the period from 01.01.2003 to 31.08.2007. No new adverse effects were identified.

▶ No change has been made to the SPC since the Committee's previous opinion dated 29 March 2006.

▶ The known safety profile of this proprietary medicinal product has not changed. Its long-term safety is relatively poor and is the reason for discontinuation of treatment in most cases. The most common adverse effects are cutaneous, hepatic and renal.

04.3 Usage/prescription data

The ALLOCHRYSSINE proprietary medicinal products have not been on the market since 20 April 2012. Stocks ran out in 2008 and the product was not commercially available in 2009. According to the available information on the website of the ANSM [French National Agency for Medicines and Health Products Safety],¹ the distribution of these proprietary medicinal products was suspended on 20 April 2012 and the date on which normal availability will be resumed is unknown. A comparable proprietary medicinal product (MYOCRISIN: sodium aurothiomalate) approved in the United Kingdom is available from Sanofi-Aventis France under a temporary authorisation for use by a named patient [ATU nominative in French].

04.4 Therapeutic use

The current treatment of rheumatoid arthritis involves the prescription of a fast-acting anti-inflammatory (NSAID, corticosteroid) and a disease-modifying drug to induce remission (clinical and laboratory parameters). Methotrexate (MTX) is the standard reference disease-modifying drug for rheumatoid arthritis. In the event of an inadequate response or if methotrexate is contraindicated, the following can be used depending on the presentation of the disease (clinical and laboratory parameters) and the pathophysiological predisposition of the patient:

- another standard disease-modifying antirheumatic drug (DMARD) as monotherapy or;
- a combination of standard DMARDs or;
- an anti-TNF or another biological therapy.

¹ Retrieved 27 May 2014 (information status: 14.02.2014).

Therapeutic use of gold salts:

In the absence of any current national guidelines on the management of rheumatoid arthritis, the European EULAR² (European League Against Rheumatism) recommendations updated in 2013 are followed.

In the previous version of the EULAR recommendations from 2010, gold salts had been rated alongside leflunomide and sulfasalazine as first-line options when MTX is contraindicated or is not tolerated, but this was rescinded in the 2013 update. While their efficacy was not questioned (this is still considered comparable to that of MTX in clinical, functional and structural terms), they are nowadays very rarely used and are indeed unavailable in many countries.

The French Society of Rheumatology was asked by the Transparency Committee office to provide a ruling on the role of synthetic DMARDs in the treatment of RA. The opinion of this learned society was that “ALLOCHRYSSINE (aurotioprol) is problematic because this medicinal product is no longer recommended and no longer initiated in the treatment of rheumatoid arthritis. There are, however, still some patients being treated with this medicinal product in France. Its withdrawal would not be a disaster.”

It should be noted that gold salts were excluded from the most recent update of the recommendations of the American College of Rheumatology (ACR)³ owing to their rarity of use and the absence of new data.

Taking account of these points, the Committee considers that the role of gold salts (ALLOCHRYSSINE) in the therapeutic strategy of rheumatoid arthritis has changed since the last renewal of inclusion by the Committee on 29 March 2006: **they no longer have a role in the treatment of RA.**

05 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee believes that the conclusions of its previous opinion of 29 March 2006 should be modified as follows:

05.1 Actual benefit:

- ▮ Rheumatoid arthritis is a serious and debilitating chronic disease.
- ▮ ALLOCHRYSSINE is intended as symptomatic treatment.
- ▮ Its efficacy/adverse effects ratio is modest.
- ▮ There are numerous treatment alternatives (synthetic and biological DMARDs).
- ▮ Gold salts no longer have a role versus currently available treatments as DMARDs in rheumatoid arthritis.

² 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.

³ 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.

Taking account of these points, the Committee considers that the actual benefit of ALLOCHRYSSINE is insufficient compared with the available alternatives to justify reimbursement by National Health Insurance in the indication “Long-acting symptomatic treatment of chronic inflammatory rheumatic diseases, in particular rheumatoid arthritis”.

05.2 Transparency Committee recommendations:

The Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance in “Long-acting symptomatic treatment of chronic inflammatory rheumatic diseases, in particular rheumatoid arthritis”.

Given that ALLOCHRYSSINE is judged to have an insufficient AB in the indication of the Marketing Authorisation and taking account of the arguments on which this conclusion was based, the Committee likewise does not recommend continued inclusion on the list of medicines approved for hospital use.