Examination of the dossier of medicinal products included on the reimbursement list for a period of 5 years from 30 August 2005 (Journal Officiel of 28 April 2006)

**ARAVA 10 mg, film-coated tablet**
B/30 (CIP code: 354 164-7)

**ARAVA 20 mg, film-coated tablet**
B/30 (CIP code: 354 169-9)

**ARAVA 100 mg, film-coated tablet**
B/3 (CIP code: 354 171-3)

**Applicant: SANOFI AVENTIS**

Leflunomide
ATC code: L04AA13

List I

Medicine requiring special monitoring during treatment. Prescription restricted to specialists in rheumatology and internal medicine.

Date of Marketing Authorisation: 02 September 1999 (centralised)

Date of the last Marketing Authorisation amendment: 27 January 2010 (addition of a risk management plan following the granting of a generic Marketing Authorisation for Leflunomide Winthrop which was the subject of an RMP)

**Reason for request:** Renewal of inclusion on the list of medicines refundable by National Health Insurance.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Leflunomide

1.2. Indications
“Leflunomide is indicated for the treatment of adult patients with:

- Active rheumatoid arthritis as a “disease-modifying antirheumatic drug” (DMARD)
- Active psoriatic arthritis

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching.”

1.3. Dosage
“The treatment should only be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) and a complete blood cell count, including a differential white blood cell count and a platelet count, must be checked simultaneously and at the same frequency: before starting leflunomide treatment, every 2 weeks during the first 6 months of treatment, and every 8 weeks thereafter.

Leflunomide treatment should start with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily. Patients may be started on leflunomide 10 mg or 20 mg depending on the severity (activity) of the disease. The recommended maintenance dose for patients with psoriatic arthritis is 20 mg once daily.

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months of treatment.

No dose adjustment is recommended in patients with mild renal insufficiency.

No dosage adjustment is required in patients over 65 years of age.

ARAVA is not recommended for use in patients under 18 years of age since efficacy and tolerance in juvenile rheumatoid arthritis (JRA) have not been established.”
2 REMINDER OF THE COMMITTEE’S OPINIONS AND CONDITIONS OF INCLUSION

Committee’s opinion of 12 April 2000

Opinion on listing in rheumatoid arthritis.

The actual benefit of these medicinal products is substantial.

In patients who fail to respond to any of the usual disease-modifying treatments, ARAVA provides a modest level III benefit in relation to comparator medicines.

As first line treatment, since its short-term efficacy/tolerance ratio is no better than that of sulfasalazine or MTX, and bearing in mind that follow-up is limited to 2 years, ARAVA does not provide any improvement in actual benefit compared with these medicines.

In patients who are unable to tolerate or have contraindications to MTX, this medicinal product provides a modest level III improvement in actual benefit.

Committee’s opinion of 23 July 2003

Application to change the target population.

The Committee examined the new data on the target population for this medicinal product mentioned in the opinion of 12 April 2000 and issued the following opinion:

The prevalence of rheumatoid arthritis is around 130,000 to 240,000 patients.

A disease-modifying treatment is needed by 55% to 65%. The population falling within the indication which the Committee recommended for inclusion in its opinion of 12 April 2000 is 71,500 to 156,000 patients.

25% to 45% of patients with a diagnosis of RA are treated with MTX.

18% of patients treated with MTX did not respond to treatment.

The population of patients for whom, according to the Committee’s opinion of 12 April 2000, ARAVA provides a modest improvement in actual benefit (failure to respond to the usual disease-modifying treatment) would be between 6,000 and 19,500 patients.

Committee’s opinion of 10 November 2004

Opinion on inclusion in psoriatic arthritis.

The actual benefit of these medicinal products is substantial.

In patients who do not respond to, cannot tolerate or have contraindications to disease-modifying treatments, ARAVA provides a modest level III improvement in actual benefit compared with no treatment.

Committee’s opinion of 14 December 2005

Opinion on renewal of listing.

The actual benefit of these medicinal products is substantial.
3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2010)
L : Antineoplastic and immunomodulating agents
04 : Immunosuppressants
A : Immunosuppressants
A : Selective immunosuppressants
13 : Leflunomide

3.2. Medicines in the same therapeutic category
None

3.3. Medicines with a similar therapeutic aim
These are other disease-modifying treatments for rheumatoid arthritis and psoriatic arthritis.

Disease-modifying treatments for rheumatoid arthritis

- Medicinal products based on methotrexate (MTX), sulfasalazine, gold salts, azathioprine, D-penicillamine and tiopronin.
- Anti-TNFα: adalimumab (HUMIRA), etanercept (ENBREL), infliximab (REMICADE) and certolizumab (CIMZIA).
- Other biotherapies: abatacept (ORENCIA), anakinra (KINERET), rituximab (MABTHERA) and tocilizumab (ROACTEMRA).

Disease-modifying treatments for psoriatic arthritis

- MTX,
In practice, other disease-modifying treatments which do not have marketing authorisation in this indication are used, particularly sulfasalazine.
- Anti-TNFα: adalimumab (HUMIRA), etanercept (ENBREL) and infliximab (REMICADE).
4.1. Efficacy

4.1.1 Rheumatoid arthritis (RA)

In the indication RA, the company has submitted the results of:

- An open-label study\(^1\) evaluating the efficacy of the combination ciclosporin + leflunomide (LEF) versus each of the active ingredients as monotherapy in 106 patients with RA and methotrexate (MTX) treatment failure. The primary endpoint was the percentage of ACR20, ACR50 and ACR70 responders\(^2\). After 1 year of treatment with ciclosporin in a dosage of 2.5 to 5 mg/kg/day (n = 35) or leflunomide 20 mg/day (n = 36) or a combination of these two active ingredients (n = 35), no differences in the ACR20 criterion were found between the groups. A difference in the ACR50 and ACR70 criteria in favour of the fixed combination was found. Because of its open-label design, no conclusion can be drawn from this study.

- An observational study performed using a New Zealand data registry on the use of LEF\(^3\). Data were available for 244 patients who were monitored for 2 years. The majority of the monitored population was female (76.3%), while the mean age was 57.4 years and 96.1% of patients had RA. The other diseases were psoriatic arthritis (2.6%) and idiopathic juvenile arthritis (1.3%). All patients had previously been treated with one or more classic disease-modifying treatments such as MTX; they were treated with LEF because they either could not tolerate or failed to respond to an earlier disease-modifying treatment. About 30.3% of patients received LEF as monotherapy. The rates for maintenance on LEF were 64% at 1 year and 49.4% at 2 years. The reasons for stopping treatment were adverse effects for 58.1% of patients, loss of efficacy for 26.9% of patients and other reasons for 15%.

- An observational study\(^4\) performed in Warsaw in 78 patients with active RA. The objective of the study was to compare the efficacy of treatment with MTX, LEF and anti-TNF\(\alpha\) (etanercept or infliximab) + MTX on RA activity. The patients were treated for 24 weeks with:
  - MTX 15 mg/week (n = 30),
  - LEF 20 mg/day (n = 30), or
  - Anti-TNF\(\alpha\) (etanercept 25 mg 2x/week or infliximab 3 mg/kg in weeks 0, 2, and 6 then every 8 weeks) + MTX 15 mg/week (n = 18).

No primary endpoint was defined. In view of its observational design, no robust conclusion concerning efficacy can be drawn from the results of this study.

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\(^2\) The ACR (American College of Rheumatology) score is used to evaluate a patient’s response to treatment. It takes into account the number of painful joints, the number of instances of synovitis, the pain as assessed by the patient, the global assessment by the patient and the doctor, functional status and laboratory inflammation markers. The ACR 20response, for example, corresponds to a 20% improvement in the number of swollen and painful joints and a 20% improvement in at least three of the following parameters:
  - ESR or CRP (C-reactive protein)
  - Disease activity assessed by the patient on a VAS
  - Disease activity assessed by the doctor on a VAS
  - Pain assessed on a VAS
  - Disability index


A combined analysis of two open extension studies designed to evaluate radiographic progression beyond 2 years in the patients treated with LEF among the 824 patients included in the phase III studies that led to the Marketing Authorisation of leflunomide; 128 were included in this follow-up. The results of this study were based on a historical comparison between the radiological score on inclusion (assessed before starting leflunomide) and the radiological score at final assessment; no conclusion can be drawn from them.

Overall, the new data presented are of little relevance; they provide no new information enabling to determine the place of leflunomide in the management of RA, particularly compared with anti-TNFαs.

4.1.2 Psoriatic arthritis (PA)
No new efficacy data were submitted in the psoriatic arthritis indication. A tolerance study was provided and details are given in section 4.2 below.

The results of an observational study that was not requested by the transparency Committee were supplied (see appendix).

4.2. Tolerance
Cumulative exposure to ARAVA (leflunomide) worldwide from 11 September 2004 to 10 September 2009 was estimated to be 928,179 patient years, including 59,729 patient years in France. An analysis of the pharmacovigilance data available since ARAVA was placed on the market gave rise to changes to the SPC.

The changes to the SPC concerning tolerance made since the last opinion are shown below:

- 19 September 2005: change in the frequency of severe infections including septic conditions, from very rare to rare.
- 10 January 2006: addition of necrotising cutaneous vasculitis as a very rare adverse effect.
- 08 November 2007: addition of renal impairment as an adverse effect with indeterminate frequency.
- 28 October 2009: Pregnancy section updated to include the conclusions of the OTIS study: “In a prospective study in 64 women who accidentally became pregnant while being treated with leflunomide, with exposure to leflunomide for no more than 3 weeks after conception, and who underwent an active metabolite elimination procedure, no significant difference (p = 0.13) was observed in the rate of major structural abnormalities (5.4%) compared with the other groups (4.2% in the corresponding patient group [n = 108] and 4.2% in the group of healthy pregnant women [n = 78]).” The SPC still includes a contraindication in “pregnant women, or women of child-bearing potential who are not using reliable contraception during treatment with leflunomide and for as long as the plasma levels of the active metabolite are more than 0.02 mg/l. Pregnancy must be discarded before the start of treatment with leflunomide.”

Concerning cases of hepatotoxicity, the information reported in the last PSURs is consistent with that in the SPC.

The company submitted the results of a retrospective Italian cohort study designed to evaluate the tolerance of leflunomide and MTX in everyday practice in 86 patients with psoriatic arthritis. The adverse effects and reasons for stopping treatment were evaluated. At 1 year, no statistical difference was seen between the two groups concerning the percentage of treatment

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discontinuation due to adverse effects, with 29.2% in the LEF group vs 10.8% in the MTX group (p = NS).

4.3. Conclusion
As part of its application to renew ARAVA’s inclusion on the list of reimbursable medicinal products, the company supplied new data. These data do not alter the efficacy/adverse effects ratio of these medicinal products.

5 DATA ON USE OF THE MEDICINAL PRODUCT

IMS DOREMA data
According to the IMS EPPM-DOREMA panel (moving annual total to November 2009), 31,000 prescriptions were issued for these medicinal products. This small number of prescriptions does not allow any qualitative analysis to be made of the data. It should however be noted that 90% of prescriptions were for rheumatoid arthritis.

Sales data (source GERS)

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**number of boxes

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*number of tablets  
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</table>

*number of tablets  
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6.1. **Re-assessment of actual benefit**

Rheumatoid arthritis is a serious and disabling chronic disease.

Psoriatic arthritis is a chronic disease, certain forms of which can be serious and disabling.

The efficacy/adverse effects ratio for these medicines is moderate.

These medicinal products are intended as symptomatic treatment.

There are treatment alternatives.

These medicinal products retain their place as disease-modifying treatment for rheumatoid arthritis and psoriatic arthritis, particularly in patients who do not respond to, cannot tolerate or have contraindications to methotrexate.

In view of all these factors, the transparency Committee considers that the actual benefit of ARAVA continues to be substantial in the indications in the Marketing Authorisation.

6.2. **Therapeutic use**

The management of rheumatoid arthritis at present consists of the prescription of a fast-acting anti-inflammatory (NSAID or corticosteroid) and a disease-modifying medicine to induce remission in clinical and laboratory parameters.

Methotrexate is the classic reference disease-modifying treatment for rheumatoid arthritis. The maximum tolerated dosage is 25 mg/week but this must be adapted to the clinical setting and the tolerability of the treatment.

In cases where there is an inadequate response or a contraindication to methotrexate, depending on the clinical/laboratory presentation of the disease and the patient’s physiopathological condition, the following should be used:

- Another classic disease-modifying treatment as monotherapy, or
- A combination of classic disease-modifying treatments, or
- An anti-TNFα agent

Anti-TNFα medicines are used alone or in combination with methotrexate in cases where there is an inadequate response to or intolerance of disease-modifying treatments, including methotrexate. They can, according to the HAS recommendations of 2007, be used as first-line treatment in certain active and severe forms of rheumatoid arthritis.

However, according to experts, about 30% of patients have an inadequate or insufficient response to anti-TNF agents after 2 years.

In cases where anti-TNF treatment fails, the possible alternatives are:

- Use of another anti-TNF
- Use of either one of the two available “third-line” biotherapies: rituximab (a monoclonal antibody targeting B lymphocytes), abatacept (T lymphocyte co-stimulation inhibitor) or tocilizumab (a monoclonal antibody targeting interleukin-6). Tocilizumab is also indicated as second-line treatment, i.e. in cases where classic disease-modifying treatments including MTX have failed.
Therapeutic use of leflunomide (ARAVA)

ARAVA retains its place as a disease-modifying treatment for rheumatoid arthritis and psoriatic arthritis, particularly in patients who do not respond to, cannot tolerate or have contraindications to methotrexate.

6.3. Transparency Committee recommendations
The transparency Committee recommends maintaining inclusion on the list of medicinal products refundable by National Health Insurance in the indications and at the dosages of the Marketing Authorisation.

6.3.1. Packaging: Appropriate for the prescription conditions.

6.3.2. Reimbursement rate: 65%
APPENDIX

ARAVA® (leflunomide)
Aventis Pharma

DEFINITIVE RESULTS OF THE POST-LISTING STUDY
ISPEP GROUP’S OPINION OF 08/04/2010

1. CONTEXT

The Transparency Committee did not ask for any study for this medicinal product when it was included on the reimbursement list, either in 2000 for rheumatoid arthritis or in 2004 for active psoriatic arthritis. It was the Committee for the Pricing of Healthcare Products (CEPS), in the addendum signed with Aventis Pharma on 20/09/2005, which asked that a post-listing study be undertaken. The wording regarding this study was as follows: “The company undertakes to conduct a study on prescriptions for ARAVA to check whether the populations treated with ARAVA are the same as the target populations recorded by the TC:
- Patients who fail to respond to the usual disease-modifying treatment for rheumatoid arthritis
and
- Patients who fail to respond to, cannot tolerate or have a contraindication to disease-modifying treatments for psoriatic arthritis.”

The results of this study were to be sent to the CEPS within one year of the addendum being signed.

Following a reminder from the CEPS in November 2006, on 06/12/2006, the company submitted a synopsis of a study using the Thalès database and a table of results, supplementing this documentation with a letter containing arguments for choosing the Thalès database, plus new results. This post-listing dossier had been examined in the ISPEP group on 20/03/2007 and a letter of reply was sent to the company on 02/04/2007, emphasising the fact that the study’s methods had not been validated by the ISPEP group and that the results only partly met its request, particularly in the absence of data on patients’ earlier treatment and the reasons for prescriptions. These results showed, however, that use as 1st-line treatment occurred in at least 30% of cases, contrary to the transparency Committee's recommendation.

In February 2010, in its dossier applying for renewal of its listing, the company included data on the use of ARAVA® obtained in an Ipsos study (results presented below), again without having had the methods validated by the ISPEP group.

2. RESULTS PRESENTED

2.1. Comments on methods

To obtain details of how treatment with ARAVA® was initiated, the company conducted a retrospective study of patient case files held by doctors prescribing ARAVA®: 80 doctors (65 rheumatologists and 15 internists) were selected at random from the ICOMED-CEGEDIM database. The protocol made provision for the inclusion of a total 350 patients who were currently being treated or had been treated in the last 12 months: 8 patients per rheumatologist and 5 patients per internist. However, because of the small number of participating internists, the quota of patients included per doctor was increased to 10 per doctor after the start of the study.

Information about the study’s methods which can be used to assess its quality is sparse. The company, which had nevertheless already been warned in 2007, should have submitted a draft study to the ISPEP group for validation before setting up the study.

Thus, the main points regarding methods are as follows:
No guarantee is given as to how representative the doctors included in the study are of all potential prescribers of ARAVA (rheumatologists, internists, other doctors such as general practitioners, etc.). Moreover, no explanation is given on the rationale and basic theories prompting to include 65 rheumatologists and 15 internists for a total of 350 patients.

- Nor is there a guarantee that the patients included are representative, and no information is given in the dossier about how the possibility of patient selection was excluded.
- The reasons why the planned recruitment levels for rheumatologists and internists were not reached should have been given, particularly as this point could have an impact on the representative nature of the data submitted.
- No information is given on the data quality or the missing data (this point is all the more important since this is a retrospective compilation of data).
- There is no discussion on the main forms of bias inherent in this type of study (selection bias, information bias, memorisation bias, etc) of which there may be a great number, given the proposed protocol.
- The documentation level of reasons for first-line prescribing excluding contraindications is low.

2.2. Description of the doctors and their patient clientele (personal statements)

59 doctors were finally included in this study (53 rheumatologists and 6 internists). The male/female split for the doctors included is 2.5:1 and their mean age is 50 years.

For rheumatoid arthritis (RA), their patient clientele (personal statements) is about 75 cases managed per year, for which 17 are are annual new cases (23%). 30% of doctors treat at least 50 cases (up to 300) per disease-modifying treatment and 15% of doctors treat at least 50 cases (up to 150) with biotherapies.

For psoriatic arthritis (PA), 25 cases were said to be managed per year, including 7 new cases a year (28%). 22% of doctors treat more than 22 cases (up to 100) per disease-modifying treatment and 14% of doctors treat more than 20 cases (up to 90) with biotherapies. 12% of patients were said to have been referred by a dermatologist.

2.3. Description of patients on inclusion

Most of the 397 patients included were women (70%), with a mean age of 55 years, while 80% had RA and 20% had PA. The diagnosis was made 6 years ago (median) for RA and 5 years ago for PA.

The patients had been treated with ARAVA for 1 to 2 years (median), at a dosage of 20 mg in 87% of cases (12% with a dosage of 10 mg and 2% with a dosage of 30 mg).

Where patients had received an earlier treatment (276 patients, i.e. 69.6% of cases), in 62% of cases this was methotrexate. The main reasons for discontinuing this earlier treatment were failure to respond to the treatment and adverse effects.

On the other hand, 118 patients (29.7%) had not received treatment prior to ARAVA:
- 16 patients (14%) because they had a contraindication to other treatments
- 26 patients (22%) received ARAVA as disease-modifying treatment
- 76 patients (64%) received ARAVA for other reasons.

Thus, a total of 102 patients (26% of cases) received ARAVA as first-line therapy when they showed no contraindication to other treatments.

The prescription of ARAVA as first-line therapy seemed to occur mainly with PA and subjects with “mild to moderate” disease activity.

3. CONCLUSION

In view of the methodological limitations of this study, for which the protocol has still not been validated by HAS, it is impossible to give a verdict based on the data submitted. It should however be emphasised that, as in 2007, about 30% of ARAVA prescriptions are for first-line therapy, which contradicts the target populations defined by the Transparency Committee.