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## TRANSPARENCY COMMITTEE

Opinion  
23 July 2014

### PLAQUENIL 200 mg, film-coated tablet

B/30 (CIP: 34009 364 414 6 0)

Applicant: SANOFI-AVENTIS France

INN	hydroxychloroquine sulfate
ATC code (2014)	P01BA02 (synthetic antimalarials)
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>“Long-acting symptomatic treatment of rheumatoid arthritis, Discoid lupus erythematosus, Subacute lupus erythematosus, Adjuvant or preventive treatment of relapses of systemic lupus erythematosus, Prevention of polymorphous light eruption.”</b>

## 01 ADMINISTRATIVE AND REGULATORY INFORMATION

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Marketing Authorisation (national procedure)	Date initiated (national procedure): 27 May 2004
Prescribing and dispensing conditions /special status	Non-prescription medicine

ATC Classification	2014 P: Antiparasitic products, insecticides and repellents P01: Antiprotozoals P01B: Antimalarials P01BA: Aminoquinolines P01BA02: hydroxychloroquine
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## 02 BACKGROUND

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Examination 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 31.12.2009 by an Opinion published in the Official Gazette of 20.11.2009.

When inclusion was last renewed on 22 July 2009, the Committee assigned to this proprietary medicinal product a substantial AB in all indications.

## 03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

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### 03.1 Therapeutic indications

“Long-acting symptomatic treatment of rheumatoid arthritis,  
Discoid lupus erythematosus,  
Subacute lupus erythematosus,  
Adjuvant or preventive treatment of relapses of systemic lupus erythematosus,  
Prevention of polymorphous light eruption.”

### 03.2 Dosage

See SPC.

## 04 ANALYSIS OF NEW AVAILABLE DATA

### 04.1 Efficacy

Account was taken only of the relevant studies that can be used to assess the efficacy and/or therapeutic use of hydroxychloroquine in the indications of its Marketing Authorisation and published after the Committee's last Opinion of 22 July 2009.

#### 4.1.1 Rheumatoid arthritis

##### Data supplied by the company:

The company has supplied new efficacy data, in particular the results of three studies evaluating treatment strategies, the aim of which was therefore not to evaluate the efficacy of one substance in particular but to evaluate treatment models (combined treatment, sequential treatment, etc.).

##### Study by Moreland LW et al. (2012)<sup>1</sup>

The aim of this controlled, randomised, double-blind study (Treatment of Early Rheumatoid Arthritis - TEAR) was to determine if it was preferable to treat "aggressively" all patients with early severe RA with a combination of treatments or to use first-line methotrexate (MTX) as monotherapy then add-on treatment. Its aim was also to compare the combination of MTX + anti-TNF (etanercept) with triple therapy consisting of conventional disease-modifying treatments (MTX, sulfasalazine (SSZ) and hydroxychloroquine (HCQ)).

A total of 755 patients were randomised to four groups to receive:

- early aggressive treatment (n=376) with etanercept + MTX or triple therapy with MTX+SSZ+HCQ (244 patients were treated with etanercept 50 mg a week + MTX up to 20 mg/week and 132 with triple therapy MTX+SSZ+HCQ) or
- escalated treatment (n=379) starting with MTX as monotherapy then, if DAS28-ESR in wk 24  $\geq$  3.2, the addition of either etanercept (255) or SSZ+HCQ (124).

The primary efficacy endpoint was the change in DAS28-ESR between weeks 48 and 102. The analysis made was ITT.

On inclusion, the characteristics of the four groups were comparable (mean duration of the progression of RA 3 to 4 months, DAS28-ESR of  $5.8 \pm 1.1$ ). A total of 67.9% of the patients completed the 2 years of the study (no statistical difference between the groups in terms of the percentage stopping treatment), i.e. 32.9% of the percentage stopping treatment (versus 10% expected used to calculate the number of subjects required). The main reason for stopping treatment was the patient's decision (100, 42%), impression of inefficacy (n=31), lost to follow-up/unspecified reason (n=29).

In week 24 (start of escalated treatment if needed), the superiority of the two strategies with early aggressive treatment versus escalated treatment was demonstrated in terms of the reduction in the DAS28-ESR score: 4.2 versus 3.6,  $p < 0.0001$ . It should be noted that in week 24, in the escalated treatment group, 28% of patients had a DAS28-ESR of  $\leq 3.2$  and therefore continued to be treated with MTX as monotherapy; 72% were treated with either etanercept or SSZ+HCQ. In the group with early aggressive treatment, 41% of patients who received MTX + etanercept and 43% of those who received triple therapy had a DAS28-ESR of  $\leq 3.2$  in week 24.

An analysis of the primary endpoint between week 48 and week 102 showed no statistically significant difference between the four treatment groups.

No difference in terms of the reduction in radiographic progression was observed between the combined "escalated treatment" group and the combined "aggressive treatment" group. However,

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<sup>1</sup> Moreland L.W et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial, *Arthritis Rheum* 2012; 64: 2824-2835.

the superiority of the combination of etanercept + MTX versus triple therapy with MTX+SSZ+HCQ on radiographic progression in week 102 was suggested: 0.64 versus 1.69,  $p=0.047$ .

According to the authors, the initial use of MTX as monotherapy with the addition of SSZ+HCQ (or etanercept, if necessary, after 6 months) is a reasonable therapeutic strategy for the management of patients with early RA. It should be noted that 28% of patients respond to monotherapy with MTX.

Swedish SWEFOT study - Swedish Farmacotherapy Trial published in 2009 and 2012 (Van Vollenhoven RF, et al<sup>2,3</sup>).

This open randomised study<sup>4</sup> evaluated, in patients suffering from early RA (<1 year), which was active (DAS28 < 3.2) who were naive to conventional disease-modifying treatments, the benefit for patients who do not respond to MTX in a strategy with the addition of sulfasalazine (SSZ) and hydroxychloroquine (HCQ) by comparison with infliximab (IFX) 3 mg/kg every 8 weeks. The absence of response to MTX was assessed at the end of a 1st period during which all patients were treated with MTX up to 20 mg/week. After 3 to 4 months, patients with DAS28 > 3.2<sup>5</sup> were randomised to the addition of either SSZ and HCQ or IFX. The primary efficacy endpoint was the proportion of patients achieving a “good EULAR response” at 1 year. These results were published in 2009:<sup>2</sup> the proportion of patients achieving the primary endpoint was larger with infliximab 39% (50/128) than with the combination SSZ+HCQ 25% (32/130),  $p=0.0160$ . At 18 months and 2 years (results published in 2012<sup>2</sup>), there is no longer any statistical difference between the groups in terms of good EULAR response. However, in terms of radiographic progression at 2 years (total Sharp score modified by van der Heijde), a statistically significant difference in favour of the conventional treatments by comparison with infliximab was shown: mean  $7.23 \pm 12.73$  versus  $4 \pm 10$ ,  $p=0.009$ . The open design of this study limits the level of evidence of these results.

Finnish FIN-RACo study (Finnish Rheumatoid Arthritis Combination therapy trial), 11-year results published in 2012 (Rantalaiho V, et al.<sup>6</sup>)

This study (which started in 1993) with a controlled, randomised design (double-blind or open design not specified in the publication) compared, in terms of clinical remission, two treatment strategies: sulfasalazine as monotherapy *versus the* combination of methotrexate + sulfasalazine + hydroxychloroquine + corticosteroid therapy. On inclusion, 199 patients with early RA developing for a median of 6 months and naïve to DMARD were randomised and followed up. One hundred and thirty-eight (138) patients were analysed at 11 years.

The analyses made at 2, 5 and 11 years were in favour of the early triple therapy strategy without any increase in adverse effects. The monotherapy strategy too was effective, with low disease activity and moderate radiographic progression.

The FIN-RACo treatment strategy is recommended (according to the Finnish national guidelines) for 1st-line use in early RA, is adopted by Finnish doctors and results in the less frequent use of biotherapies in Finland than in other countries.

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<sup>2</sup> Van Vollenhoven R.F et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial, *Lancet* 2009; 374:459-466.

<sup>3</sup> Van Vollenhoven R.F et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial, *Lancet* 2012; 379: 1712-1720.

<sup>4</sup> Patients and investigators knew the nature of the treatment assigned.

<sup>5</sup> Corresponds to patients not achieving weak disease activity.

<sup>6</sup> Rantalaiho V et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Rheum* 2009; 60: 1222-1231.

### Additional data:

An analysis of the literature identified other studies of therapeutic strategies, particularly in the treatment of recently developing RA. These studies have been the subject of numerous successive publications (the references are not exhaustive; only those considered relevant for the assessment of efficacy with the longest follow-up were used).

The BEST study<sup>7</sup> evaluated four treatment strategies in early RA (successive monotherapy, “step-up” addition strategy, “step-down” subtraction strategy with a high initial dose of prednisone, early anti-TNF biotherapy with infliximab). After 5 years, 48% of the patients were in clinical remission (DAS < 1.6) and 14% in remission without treatment, whatever the initial treatment. The results confirm that a substantial clinical and radiographic improvement can be achieved whatever treatment strategy is initiated (including a combination of conventional disease-modifying treatments, including hydroxychloroquine) if it is adhered to strictly with the specified aim of reducing disease activity.

The COBRA study in which patients with early RA (developing for less than 2 years) were treated with either sulfasalazine as monotherapy or a combination of corticosteroid therapy in decreasing doses, methotrexate and sulfasalazine. The combination was superior to monotherapy in terms of the short-term control of disease activity and the short-, medium- and long-term control of the progression of structural lesions. The results at 11 years showed that early aggressive treatment during RA maintains a structural benefit after 11 years without any increase in morbidity.<sup>8</sup>

The randomised, single-blind tREACH study (*treatment in the Rotterdam Early Arthritis CoHort*)<sup>9</sup> compared three treatment strategies (early treatment with the combination MTX+SSZ+HCQ and an IM injection of corticosteroids (either 120 mg methylprednisolone or 80 mg triamcinolone) or early use of the combination MTX+SSZ+HCQ and oral corticosteroid therapy in decreasing doses (15 mg/day from week 1 to week 4, then 10 mg in week 5 and week 6, then 5 mg in week 7 and week 8, then 2.5 mg/day from week 9 to week 10) or finally with MTX as monotherapy and decreasing oral corticosteroid therapy). The combinations of disease-modifying treatment were superior to monotherapy with MTX.

The aim of the controlled, randomised, double-blind Danish study (CIMESTRA)<sup>10</sup> was to evaluate treatment for early RA (diagnosis < 6 months ago) with early aggressive treatment with methotrexate (MTX) as monotherapy or in combination with other conventional DMARDs (cyclosporin then, during the 2nd year, stopping cyclosporin and adding hydroxychloroquine 200 mg/day). The patients (n=160) were treated with systematic intraarticular injections of the swollen joints. Patients who had no ACR20 response, despite 20 mg methotrexate/week, received the same medicine parenterally for 3 months then triple therapy with methotrexate, sulfasalazine and hydroxychloroquine, and finally an anti-TNF treatment if disease activity persisted. After 1 year, no statistical difference was found between the monotherapy and the DMARD combination. According to the authors, the addition of hydroxychloroquine seems to have potentiated the effect of the MTX.

### NEO-Raco study<sup>11</sup>

The aim of this randomised, double-blind study was to determine whether the addition of infliximab to the FIN-RACo strategy (described earlier: combination of methotrexate + sulfasalazine +

<sup>7</sup> Klarenbeek NB et al. The impact of four dynamic; goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis in the BeSt study. *Ann Rheum Dis* 2011; 70: 1039-1046.

<sup>8</sup> Van tuyl et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 807-812.

<sup>9</sup> de Jong PH et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. *Ann Rheum Dis* 2013; 72: 72-78.

<sup>10</sup> Hetland et al. The CIMESTRA study: intra-articular glucocorticosteroids and synthetic DMARDs in a treat-to-target strategy in early rheumatoid arthritis. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S44-S49.

<sup>11</sup> leirisalo-Repo et al. infliximab for 6 months added on combination therapy in early rheumatoid arthritis : 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo study). *Ann Rheum Dis* 2013; 72: 851-857.

hydroxychloroquine + corticosteroid therapy) improved efficacy at 2 years. The primary efficacy endpoints were remission and radiographic progression. A total of 99 patients with active, untreated early RA were included to be treated using the FIN-RACo strategy then randomised to also receive either infliximab or placebo between weeks 4 and 26. At 2 years, no statistical difference was found between the FIN-RACo + infliximab strategy and FIN-RACo + placebo in terms of remission according to the modified ACR criterion (66% versus 53%) or according to the DAS28 criterion (82% in the two groups). However, a statistical difference was found in terms of sustained modified ACR remission 26% versus 10% ( $p=0.042$ ) and the mean change in the total Sharp-van der Heijde score (0.2 and 1.4;  $p=0.0058$ ).

**Overall, these studies of strategies confirmed the efficacy of strategies combining conventional disease-modifying treatments including hydroxychloroquine for the treatment of RA. They made it possible to evaluate clinical practices and were used either as a basis (taking account of their methodological limitations) for preparing recommendations (particularly EULAR 2013) on the management of this inflammatory rheumatism, or to confirm those recommendations.**

**Thus, the EULAR 2013 recommendations consider that, in patients naive to DMARDs, monotherapy or a combination of non-biological conventional disease-modifying treatments can be used with equal justification (without favouring one strategy over another). In addition, according to these recommendations, in patients who have not responded to a 1st strategy of conventional disease-modifying treatment, a second strategy can be considered if there are no adverse prognostic factors. If such factors are present, the addition of a biotherapy should be considered.**

An analysis of the literature also identified the RACAT study (O'dell 2013<sup>12</sup>)

In this controlled, randomised double-blind study, the non-inferiority of the triple therapy MTX, sulfasalazine and hydroxychloroquine was evaluated by comparison with the combination of etanercept + MTX in 353 patients with active RA despite treatment with MTX. At the end of 24 weeks, patients without a reduction in DAS28 of  $< 1.2$  changed treatment but remained blinded. The primary endpoint was the change in DAS28 at week 48 with a non-inferiority threshold set at 0.8 (corresponding to 50% of 1.2 which is the minimum clinically relevant improvement).

Non-inferiority was demonstrated: the mean reduction in DAS28 at week 48 was -2.12 for triple therapy versus -2.29 for ETA+MTX. No difference was found between the two groups in terms of radiographic progression (secondary endpoint).

## **Conclusion**

All these data confirm the efficacy of hydroxychloroquine in combination with other non-biological, conventional disease-modifying treatments (combinations with methotrexate and sulfasalazine being the most widely studied) and alone or in combination with corticosteroid therapy in the treatment of active rheumatoid arthritis. The non-inferiority of the triple therapy MTX, sulfasalazine and hydroxychloroquine was demonstrated by comparison with the short-term (48 weeks) combination of anti-TNF (etanercept) + MTX biotherapy.

### **4.1.2 Lupus**

The company has supplied two new collections of clinical data:

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<sup>12</sup> O'Dell JR et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013; 369: 307-318.

### Ruiz-Irastorza meta-analysis and systematic review of the literature published in 2010<sup>13</sup>

Its aim was to analyse all the published data on the efficacy and safety of antimalarials (chloroquine and hydroxychloroquine) in the treatment of systemic lupus erythematosus. Controlled randomised clinical studies and observational studies published in English between 1982 and 2007 were selected (a total of 95 articles). The effects of antimalarials on disease activity, the lipid profile, bone metabolism, atherosclerosis, thrombosis, irreversible organ lesions and survival were assessed. The results suggested a beneficial effect and satisfactory safety of antimalarials, including in pregnant women.

### Publication of the French PLUS study (Costedoat-Chalumeau et al, 2013)<sup>14</sup>

The aim of this multicentre, placebo-controlled, randomised, double-blind study was to compare, in terms of the reduction in inflammatory events, a standard treatment and a treatment adjusting the doses of hydroxychloroquine so as to maintain a residual plasma concentration of  $\geq 1000$  ng/ml. A total of 573 patients with stable lupus (SELENA-SLEDAI  $\leq 12$ ) treated with HCQ for at least 6 months were included. Patients with a plasma concentration of HCQ between 100 and 750 ng/ml were randomised to one of two groups: no change in dosage or increase in the dosage of HCQ to achieve the specified aim (residual plasma concentration  $\geq 1000$  ng/ml). The primary efficacy endpoint was the proportion of patients with inflammatory events during the 7 months of follow-up. Overall, the mean plasma concentration of HCQ was  $918 \pm 451$  ng/ml. A total of 171 patients were randomised and followed up for 7 months. The proportion of inflammatory events was similar: 25% "with no change in dosage" vs 27.6% in the group with adjustment;  $p=NS$ . The authors concluded that the adjustment in the dosages of HCQ was not associated with a reduction in episodes of lupus.

#### 4.1.3 Polymorphous light eruption

No new clinical data have been supplied by the company.

## 04.2 Safety/Adverse effects

► The company has supplied new safety data covering the period from 01.05.2007 to 30.04.2012).

► Since the last renewal Opinion of 22 July 2009, changes have been made to the SPC for PLAQUENIL, in particular:

"Section 4.4 Special warnings and precautions for use": update of the recommendations on excipients with a known effect according to the current AFSSAPS [French Healthcare Product Safety Agency] guideline and update of the wording "Medicines and G 6PD deficiency" in accordance with the new standard put on line on the AFSSAPS website on 25 February 2008.

Section 4.5 Interaction with other medicinal products and other forms of interaction: update in accordance with the current interactions thesaurus

Section 4.8 Undesirable effects: addition of the following effects: abnormal colour vision; vomiting; haematological disorders such as: anaemia, aplastic anaemia, leuconetropenia and thrombocytopenia; urticaria, angioedema and bronchospasm.

Other changes to the SPC which have not yet been validated are being assessed by the ANSM [French National Agency for Medicines and Health Products Safety], including in particular the addition of information on cases of DRESS and pneumopathy reported with hydroxychloroquine and chloroquine.

► **Overall, these data do not seem likely to change the known safety profile of PLAQUENIL.**

<sup>13</sup> Ruiz-Irastorza et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010; 69: 20-28.

<sup>14</sup> Costedoat-Chalumeau et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). *Ann Rheum Dis* 2013; 72: 1786-1792.

## 04.3 Usage/prescription data

According to IMS data (moving annual total, winter 2013), 123,423 prescriptions were issued for PLAQUENIL proprietary medicinal products, including 42,500 in RA.

## 04.4 Therapeutic use

### 4.4.1 Rheumatoid arthritis

The management of rheumatoid arthritis at present consists of the prescription of an immediate-acting anti-inflammatory (NSAID, corticosteroid, etc.) and a disease-modifying medicine so as to induce clinical and laboratory remission. Methotrexate is the reference conventional disease-modifying medicine for rheumatoid arthritis. If there is an inadequate response to methotrexate or if it is contraindicated, depending on the clinical and biochemical presentation of the disease, and the patient's pathophysiological background, use is made of:

- another conventional disease-modifying treatment as monotherapy, or
- a combination of conventional disease-modifying treatments, or
- an anti-TNF agent.

#### Role of hydroxychloroquine in the therapeutic strategy:

In the absence of any current national recommendations on the management of rheumatoid arthritis, the European recommendations of EULAR<sup>15</sup> (European League Against Rheumatism) were taken into account.

They recommend sulfasalazine and leflunomide as a first-line alternative to methotrexate if that substance is not tolerated or is contraindicated.

The antimalarials hydroxychloroquine and chloroquine are no longer included in the recommendations but the rationale states that they are used in RA, particularly in combination, but also in monotherapy in patients with moderate disease activity. They have the advantage that they can be used during pregnancy but have a moderate disease-modifying effect. Their effect in terms of slowing down radiographic progression seems to be less than that of other DMARDs (methotrexate, sulfasalazine and leflunomide), which is why they are not widely offered in these recommendations, even though patients with weak disease activity are fairly unlikely to have joint degradation.

The French Society of Rheumatology (SFR) was asked by the TC office for a statement on the use of non-biological disease-modifying medicines in the treatment of RA. Hydroxychloroquine (PLAQUENIL) continues to be indicated in benign forms and in combination with other disease-modifying medicines.

The recommendations of the American College of Rheumatology (ACR) of 2012<sup>16</sup> include hydroxychloroquine among the conventional DMARDs, for the same reasons as methotrexate, leflunomide and sulfasalazine.

Data from the strategy studies described in section 1.4 showed the efficacy of hydroxychloroquine in combination with methotrexate and sulfasalazine in terms of the reduction in symptoms and the inhibition of radiographic progression in early active forms of rheumatoid arthritis.

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<sup>15</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>16</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.

In view of this information and of the available alternatives, the Transparency Committee believes that the place of hydroxychloroquine in the therapeutic strategy for managing RA, as defined in its Opinion of 22 July 2009, has changed: **it has a place in the disease-modifying treatment of benign, minimally active forms of rheumatoid arthritis and in combination with other disease-modifying treatments.**

#### 4.4.2 Lupus<sup>17,18,19,20</sup>

The aims of treating lupus are to treat the acute episodes, minimise the risks of inflammatory flares and to slow down the progression of the disease.

Hydroxychloroquine and non-steroidal anti-inflammatories are indicated in the moderate forms; corticosteroids and immunosuppressants are reserved for more severe cases; some biotherapies can be used in patients who have not responded to the usual treatments.

##### Role of hydroxychloroquine:

Hydroxychloroquine has been used in the treatment of lupus for more than 50 years with an efficacy/adverse effects ratio which is considered satisfactory. Guidelines on the ophthalmological follow-up of patients treated with hydroxychloroquine are available (ophthalmological examination during the 1st year of taking the treatment then every year, starting after 5 years of taking the treatment, to detect any retinopathy).

#### 4.4.3 Polymorphous light eruption

Since polymorphous light eruption is a disease which frequently recurs after exposure to sunlight, the treatment strategy is based mainly on preventing relapses. It combines mechanical photoprotection, non-drug measures and drug prophylaxis. Among the drug treatments for preventive use, synthetic antimalarials (hydroxychloroquine 400-600 mg/day or chloroquine 200-300 mg/day) are used as first-line treatment. They must be started 7 days before exposure to sunlight starts, then continued for the first 2 weeks. As second-line treatment, para-aminobenzoic acid is an alternative to synthetic antimalarials. Phototherapy or PUVA therapy can be suggested if properly conducted preventive treatment fails.

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<sup>17</sup> Haute Autorité de Santé, Guide – Affection de Longue Durée, Lupus érythémateux systémique, protocole national de diagnostic et de soins [HAS Guide – Chronic condition, Systemic lupus erythematosus, National Diagnosis and Treatment Protocol], January 2010.

<sup>18</sup> Van Vollenhoven R.F et al. treat-to-target in systemic lupus erythematosus recommendations from an international task force. *Ann Rheum Dis* 2014; 73: 958-967.

<sup>19</sup> Costedoat-Chalumeau et al. hydroxychloroquine dans le traitement du lupus : le renouveau. *La revue de médecine interne* 2008; 29: 735-737.

<sup>20</sup> Orphanet. consulted in June 2014.

## 05 TRANSPARENCY COMMITTEE CONCLUSIONS

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In view of all the above information, and following the debate and vote, the Committee considers that the conclusions in 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.
- ▶ PLAQUENIL (hydroxychloroquine) is intended as symptomatic treatment.
- ▶ The efficacy/adverse effects ratio of PLAQUENIL remains high in the disease-modifying treatment of RA.
- ▶ There are numerous treatment alternatives, particularly other biological and non-biological disease-modifying treatments.
- ▶ This proprietary medicinal product has a place in the disease-modifying treatment of benign, minimally active forms of rheumatoid arthritis and in combination with other disease-modifying treatments.

**Taking account of these points, the Committee considers that the actual benefit of PLAQUENIL remains substantial in benign, minimally active forms of RA and in combination with other disease-modifying treatments.**

#### 5.1.2 Lupus

- ▶ Lupus erythematosus is the name given to all the conditions forming a continuous spectrum, ranging from an isolated lesion to a serious multisystem disorder. Apart from cutaneous lesions, lupus manifests as vascular and nonvascular lesions. The systemic manifestations are of an articular, serous, renal, neurological and haematological nature. The vital prognosis depends on the presence of certain severe digestive disorders, the risk of infection and the cardiovascular complications.
- ▶ PLAQUENIL is intended as symptomatic treatment.
- ▶ Its efficacy/adverse effects ratio remains high.
- ▶ This proprietary medicinal product is indicated as disease-modifying treatment for systemic lupus erythematosus in the absence of any organ involvement requiring major treatment (corticosteroid therapy, immunosuppressants) and cutaneous lupus if local treatments fail.
- ▶ There are medicinal and non-medicinal alternatives to this proprietary medicinal product.

**Taking account of these points, the Committee considers that the actual benefit of PLAQUENIL remains substantial in the treatment of discoid and subacute lupus erythematosus and in the adjunctive or preventive treatment of relapses of systemic lupus erythematosus.**

### 5.1.3 Polymorphous light eruption

► Polymorphous and benign summer light eruptions are idiopathic forms of photodermatitis which are the commonest types of photodermatitis. The disease may recur over several years and sometimes in a more serious form. The discomfort caused may impair patients' quality of life.

► PLAQUENIL is intended as preventive treatment for relapses.

► Its efficacy/adverse effects ratio remains high.

► This proprietary medicinal product is indicated as first-line treatment in the strategy of preventing relapses of polymorphous light eruptions, in addition to standard photoprotection measures which must be systematically combined with it.

► There are medicinal and non-medicinal alternatives to this proprietary medicinal product.

**Taking account of these points, the Committee considers that the actual benefit of PLAQUENIL remains substantial in the prevention of polymorphous light eruptions.**

## 05.2 Transparency Committee recommendations:

**The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications in the Marketing Authorisation.**

► **Proposed reimbursement rate: 65%**

► **Packaging:**

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