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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need of the guideline on clinical investigation of medicinal products for the treatment of gout

Agreed by Rheumatology Immunology Working Party	April 2012
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Start of public consultation	14 June 2012
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Comments should be provided using this template. The completed comments form should be sent to R-IWP@ema.europa.eu

Keywords	Gout, clinical development, CHMP, EMA, concept paper

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1. Introduction

At present no CHMP Guideline has been elaborated for the clinical development of medicinal products aiming at prevention and/or treatment of gout and/or hyperuricaemia (e.g. urate lowering therapy (ULT) to treat or prevent acute gout flares). In the last years efforts have been made in that field with regard to the development of new products with an improved efficacy profile. Changed recommendations for treatment, prevention and diagnosis of gout have been published (EULAR/ British Society for Rheumatology (BSR) 2006, ACR (oral presentation will be published in 2012). Patient-reported Outcomes in Chronic Gout (OMERACT 10) were presented. In addition, prevalence of patients suffering from gout is increasing in Europe, at least in the UK and in Germany, in the last two decades. Therefore, a CHMP guidance is needed to express the current state of scientific knowledge in this guideline.

2. Problem statement

Gout is a type of inflammatory arthritis induced by deposition of monosodium urate crystals within joints and other tissues. It is strictly associated with hyperuricaemia, a highly heritable trait, which is defined as a serum urate level ≥6.8 mg/dL, the limit of urate solubility at physiological temperature and pH. Hyperuricaemia that is caused by ingestion of purines or fructose-rich diet, overproduction of urate or, more commonly, by renal urate under-excretion is necessary but not sufficient to cause gout. Indeed, 10-15% of subjects with hyperuricaemia will develop gout.

Two phases of gout can be distinguished: 1) acute attacks of gout more and less frequent 2) chronic phase with acute flares that become more frequent, polyarticular forms with joint involvement and crystal deposition (tophi) in soft tissues, joints or kidneys. With inadequately treated hyperuricaemia, progress of disease is most likely. Factors that affect the rate of progression to chronic gout include inadequate ULT, renal impairment, co-morbidities, lifestyle and concomitant medication. Chronic gout is associated with chronic pain, joint deformities and/or joint destructions as well as disability and reduced quality of life.

The prevalence of gout is 3.9% of adults (5.9% in men and 2% in female patients) and increases with age to rates up to 9%-12.6% in patients aged over 70 years. Hyperuricaemia is a key risk factor for gout and can result from increased dietary ingestion, increased cell turnover and/or decreased renal excretion, the latter being the predominant contributor to most cases with gout.

The aims of treatments for gout are 1) to terminate acute attacks and 2) to prevent recurrent flares and the development of complications 3) to prevent paradoxical flares during urate lowering therapy and 4) to treat the complications of chronic tophaeous gout.

Oral colchicine and/or NSAIDs as monotherapy or in combination are first line agents for systemic treatment of an acute attack of gout; steroids can also be used. Use and dosage of these first line agents can be markedly limited due to co-morbidities (e.g. chronic kidney disease, cardiovascular diseases, diabetes, arrhythmia, gastrointestinal diseases), contra-indications, or side effects. Urate-lowering therapy such as allopurinol, a xanthine oxydase inhibitor (XOI) is indicated in patients with recurrent attacks, gouty arthropathy, tophi, radiographic changes of gout, multiple joint involvement, or nephrolithisasis. Other ULTs include uricosurics (probenecid, benzbromarone, sulfinpyrazone). For prevention of crystal formation serum uric acid levels below the saturation point for monosodium urate (≤6 mg/dL or 360 µmol/L) (note the latest guideline from the British Society for Rheumatology proposes a target sUA concentration <300 µmol/L (5 µmg/dL) to increase crystal dissolution) should be maintained for life.

New agents for the treatment of gout were developed as febuxostat (another XOI), rasburicase and pegloticase. The classes of xanthine oxidase inhibitors, uricosuric agents and uricases have all been licensed for lowering serum urate levels.

A need is identified to elaborate the regulatory guidance on the clinical development of medicinal products intended for the treatment of gout.

3. Discussion (on the problem statement)

- Secondary prophylaxis
- Acute treatment (single or multiple)
- ULT
- Reversal of gouty deposits

The main topics to be discussed when preparing the guidance document are:

1. Primary endpoints (serum uric acid levels or clinically relevant endpoints?).
2. Clinically meaningful endpoints to confirm data from laboratory outcome (new patient reported outcomes (OMERACT 10)).
3. First, second and third line indication.
4. Duration of studies necessary for proposed indications ‘treatment of acute flare”, or “prevention or reduction of flares’ and of intended claims ‘symptom modifying effect’ (e.g. ‘reduction of tophi’or “slowing progression of joint destruction”.
5. Study designs (e.g. add on, drug free intervals).
6. Different study populations:
    a) Patients unresponsive/intolerant to standard therapy for:
        - acute attack treatment,
        - urate lowering agents
    b) Subgroups of specific interest:
        - elderly patients, subjects with chronic kidney disease (CKD 2-5)
        - patients with severe treatment refractory gout,
7. How to adequately consider baseline characteristics, co-morbidities and co-medication in patients with severe recurrent gout?
8. Safety, especially in terms of CV events.

4. Recommendation

It is proposed to elaborate a CHMP Guideline addressing the clinical investigation of medicinal products for the treatment of gout in order to achieve a European common position on the above-mentioned issues.

5. Proposed timetable

It is anticipated that a new draft CHMP Guideline may be available 9 months after adoption of the concept paper. The draft CHMP guideline will then be released for 6 months for external consultation and following receipt of comments it will be finalised in approximately 3 months.

6. Resource requirements for preparation

The preparation of this Guideline will involve the RIWP, including one Rapporteur and one Co-Rapporteur. It is anticipated that at least four plenary session discussions at the RIWP will be needed.

7. Impact assessment (anticipated)

The elaboration of the Guideline on clinical investigation of medicinal products for the treatment of gout will be helpful to achieve consensus in the evaluation of such products by regulatory authorities. Furthermore, it is expected that such guidance document would improve quality and comparability of submitted studies by pharmaceutical industries.

8. Interested parties

It is envisioned to contact EULAR.

9. References to literature, guidelines, etc.

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