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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
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DRAFT

**GUIDELINE ON THE DEVELOPMENT OF NEW MEDICINAL PRODUCTS FOR THE
TREATMENT OF ULCERATIVE COLITIS**

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Comments should be provided using this [template](#) to line.jensen@emea.europa.eu

Fax +44 20 7418 8613

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EXECUTIVE SUMMARY

This Guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with ulcerative colitis. It should be read in conjunction with Directive 2001/83/EC, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95)
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96)
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety (CHMP/ICH/375/95)
- Reflection Paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products (CHPM/EWP/139391/04)
- Points to Consider on Application with 1) Meta-analyses and 2) One Pivotal Study (CHPM/2330/99)
- Guideline on the Choice of the Non-Inferiority Margin (CHMP/EWP/2158/99)
- Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (CHMP/PhVWP/235910/05)

1. INTRODUCTION (BACKGROUND)

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease affecting the colon. The prevalence is estimated as 70-150 cases per 100.000 with peak age of onset between 15 and 25 years. Ulcerative colitis also affects children, but is rare before school-age. The disease usually involves the rectum but may extend proximally to involve a portion of or the entire colon. About 40 to 50% of patients have disease that is limited to the rectum and the rectosigmoid colon, 30 to 40% have disease extending beyond the sigmoid flexure but not involving the whole colon, and 20% have total colitis.

The mainstay of therapy for mild to moderate UC is sulfasalazine and 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing remission in UC and in maintaining remission in UC. The majority of patients with moderate to severe active UC benefit from topical, oral or parenteral glucocorticosteroids. Remission, however, cannot be maintained with steroids. Azathioprine (AZA) or 6-mercaptopurine (6-MP) have been employed as glucocorticoid-sparing agents in patients unable to be weaned from glucocorticoids. One anti-TNF α agent has been approved for the treatment of UC refractory to both corticosteroids and AZA/6-MP. Surgery with colectomy is curative but is reserved for severe fulminant or resistant cases and in some cases as cancer prevention. Pouchitis is an inflammation of the ileal pouch, occurring in up to 20-30% of patients after an ileal pouch-anal anastomosis. As UC is pre-cancerous, surveillance is usually introduced after 8-10 years of disease duration with regular colonoscopies. Mortality is not increased in UC in general but the disease may present as life-threatening fulminant colitis. Extra-intestinal manifestations of UC include primary sclerosing cholangitis, as well as eye, joint and skin manifestations.

2. SCOPE

This Guideline is intended to assist applicants during the development of products for the treatment of ulcerative colitis, where no current regulatory guidance exists. It is only guidance; any deviation from guidelines should be justified. The Guideline does not address generic drug development in UC.

3. CLINICAL TRIALS

3.1. PATIENTS' CHARACTERISTICS AND SELECTION OF PATIENTS

3.1.1. Definitions and diagnostic criteria

Ulcerative colitis is a chronic, inflammatory disease of the large intestine and rectum characterized by episodes of increased stool frequency and bloody diarrhoea. The diagnosis of ulcerative colitis should be based on patient history (diarrhoea and rectal discharge of blood and/or pus), endoscopic findings (continuous oedema, friability, granularity and ulcerations in colorectal mucosa), and histological findings (crypt distortion/abscess, ulceration). Infectious causes of colitis and malignancy must be ruled out. Depending on the extent of disease, patients can be classified as having 1) distal disease involving only the rectum (proctitis) or the rectum and the sigmoid colon (proctosigmoiditis), 2) left sided disease (extending from the rectum to the splenic flexure), 3) extensive disease (extending from the rectum to the hepatic flexure) and 4) pancolitis (involving the entire large intestine). Approximately half of patients with distal disease will experience proximal extension with time. From a therapeutic point of view UC can be classified as distal disease involving the rectum accessible for topical treatment with suppositories, recto-sigmoid disease accessible for topical treatment with enemas, or disease extending beyond sigmoid colon requiring systemic treatment. Depending on the disease activity, patients can be classified as being in remission or having mild, moderate or severe active disease, e.g. according to the criteria of Truelove and Witts.

Patients with fulminant ulcerative colitis represent a special sub-group of patients with severe disease.

Refractory disease

Patients exhibiting no improvement (defined according to activity index used) despite the use of corticosteroids in an adequate dose and for an adequate time period are defined as being steroid refractory. The precise dose and duration should be pre-specified and justified. Patients are refractory to azathioprine/6-mercaptopurine if they do not respond to a sufficient dose within 3 to 6 months of treatment start.

Steroid dependency

Patients exhibiting response to steroids but having flare on tapering (precluding steroid withdrawal) should be classified as being steroid dependent. Precise criteria for minimum duration of treatment and dose should be pre-specified and justified. Merely the use of corticosteroids at baseline is not equal to steroid-dependency.

3.1.2. Inclusion criteria/Exclusion criteria

Only patients having definite ulcerative colitis should be included in trials. Extent as well as severity of the disease should be defined by recent clinical and endoscopic evaluation. The inclusion criteria should define the study population in terms of severity and extent of the disease in addition to previous and present therapy. The study population should reflect the specific aim of treatment (induction of remission or maintenance of remission), as well as the type of treatment (systemic or topical) of the investigational drug. In general, it would be relevant to study either distal disease (proctitis or proctosigmoiditis) or disease involving more proximal sections of the large bowel (leftsided, extensive and pancolitis combined), as the former groups are mainly treated with rectal topical treatment whereas the latter requires systemic treatment with or without topical treatment. Usually, mild, moderate and severe disease should be studied separately as standard therapy and thus choice of comparator varies between these groups. Depending on the level of treatment (first line, second line, add-on) it may also be relevant to exclude (or specifically include) patients having failed previous treatment. If treatment is aimed at steroid refractory or steroid dependent patients, clear definitions of these conditions are required and inclusion/exclusion criteria should reflect these definitions. Similarly, if the investigational drug is being developed for treatment of patients not responding/intolerant to previous immunomodulatory therapy adequate definitions of intolerance/inadequate response should be provided.

Patients with suspicion of Crohn's enterocolitis, indeterminate colitis, ischaemic colitis, radiation colitis as well as microscopic colitis should be excluded. For new therapies, which have an immunosuppressive effect, it may be necessary to screen for certain gastrointestinal infections and exclude patients with evidence of such infections.

3.1.3. *Baseline characteristics*

In addition to standard baseline characteristics such as age/gender/body weight, the duration, extent and severity of the disease should be recorded. Concomitant therapy and previous therapy should be carefully registered.

3.2. **METHODS TO ASSESS EFFICACY**

3.2.1. *Efficacy criteria in exploratory studies*

These do not deviate from those of main therapeutic studies.

3.2.2. *Efficacy criteria in main therapeutic studies*

Primary efficacy endpoint

The endpoints used could be the same regardless of the extent of disease, but may differ in sub-populations such as refractory and steroid dependent disease. The primary endpoint should reflect disease activity in UC. There are a number of clinical activity indices for use in UC trials]. Generally, these have not been rigorously validated. Indices including signs and symptoms are preferable. Endoscopy may or may not be a part of the index. Since endoscopic appearance correlates to signs and symptoms and to biochemical measures of inflammatory activity, it is not compulsory to include endoscopy in the primary efficacy scores (potential confounding of endoscopy, time lag, observer variation). However, endoscopic appearance is a relevant secondary endpoint (see below).

- **Treatment of active disease.** The therapeutic goal is to induce remission. The precise definition of remission depends on the scales/index used but should represent a normalisation of stool frequency and absence of blood in stools. This should be obtained within 4 to 8 weeks of initialisation of therapy as suggested by the pharmacodynamics properties of the therapeutic agent. For studies of add-on in patients on steroids a scheduled steroid taper should be considered mandatory. Colectomy rate at 12 months is the relevant parameter in studies of patients with active, severe disease failing usual medical therapy. For steroid dependent patients, remission and ability to discontinue steroid treatment should be co-primary endpoints. For steroid refractory patients, the primary endpoint should be induction of remission.
- **Maintenance of remission.** Patients included should be in clinical and endoscopic remission at entry. The primary efficacy parameter should be proportion of patients maintaining remission throughout the period. Clinical relapse should be distinguished from acute infectious disease but need not be confirmed by endoscopy. For patients on steroids at entry steroids must be discontinued within the study period according to a pre-specified schedule and not reinstated for at least 6 months.

Secondary efficacy endpoints

Individual components of the activity indices may be used as secondary endpoints. Endoscopic appearance is a relevant secondary endpoint. Other secondary endpoints could include changes in stool frequency, disappearance of visible blood in faeces, normalisation of C-reactive protein and/or other acute phase reactants and quality of life. Response to treatment is only to be considered as a secondary endpoint and should be defined in advance. For steroid dependent disease reduction of steroid dose is an important secondary parameter. Histological scores can be included as a secondary efficacy parameter.

3.3. **STRATEGY AND DESIGN OF CLINICAL TRIALS**

Aim of treatment

The aim of pharmacological intervention in UC is to induce remission and to prevent relapses (maintenance of remission) and the labelling will be reflected accordingly. It cannot be assumed that a medicinal product that is effective in inducing remission is also effective in preventing relapses once remission is achieved. Therefore, both indications will have to be studied separately in Phase III trials. Modified indications are possible for certain sub-groups of patients such as steroid refractory or steroid dependent patients.

Human pharmacology

Pharmacokinetic (PK) and pharmacodynamic (PD) studies using medicinal products intended for systemic use in UC do not differ from PK/PD studies in general. For locally acting products, distribution studies are necessary, e.g. by scintigraphy. It is important that locally acting products for oral intake reach the entire colon, including the rectum. Distribution of rectally applied medicinal products will also have to be studied and for enemas this may be volume dependent. The influence of concomitant diarrhoea on distribution should be studied as well. Depending on the mechanism of action, effects of mucosal inflammation on drug absorption should be addressed.

3.3.1. Exploratory studies

The aim of explorative, Phase II studies is to explore the use of the drug for the targeted indication, to estimate dosage for further confirmatory trials and to provide basis for the study design, endpoints and methodologies of the Phase III trials. The design of Phase II trials in UC should be parallel-group, double blind, placebo-controlled.

For dose-response relationship, it is recommended to use at least three doses. Different doses may be needed for induction of remission compared with prevention of relapse and this may have to be explored in separate dose-finding studies. Dose-finding for active disease may guide, but special consideration should be given to possible long-term safety issues relating to different doses.

For proof-of-concept, clinical endpoints using activity indices and endoscopy should be the primary outcome. Biomarkers can be included amongst secondary endpoints in Phase II trials. Possible direct effect of some anti-inflammatory drugs on markers of inflammation, such as CRP, is a possibility that should be taken into consideration. Exploration of markers for selection of patients into further trials and for prediction of response can be done in Phase II trial and in the future genotyping may become important in this respect.

3.3.2. Main therapeutic studies

Phase III studies in UC should be parallel group, randomised, double-blind, placebo-controlled and/or active comparator controlled studies. In general, 2 well-conducted Phase III trials will be needed for approval. The aim of the study and the study design should be relevant for the claimed indication and for clinical practice.

With regard to the indications, induction of remission and prevention of relapse, there is not a requirement for studies in both situations before marketing authorisation application. It is recommended to study induction of remission and prevention of relapse in separate trials. There is a risk with combined studies that they try to answer too many questions in one trial, making the data difficult to interpret and therefore such trials must be carefully planned, including statistical considerations. Clinically relevant and statistically significant results are expected for both phases of such trials, i.e. both the induction phase and the maintenance phase. If only remitters to the trial drug are allowed to enter and/or are evaluated for maintenance of remission (enrichment design), the labelling will reflect this.

Apart from the aim of either induction of remission or prevention of relapse, there are in clinical practice two major factors that decide the therapeutic approach, i.e. the anatomic extent and the clinical severity of the disease. Phase III trials in UC should allow separate estimation of effect in patients with different extents of disease. This can be done either by separate trials or by stratification. Patients with proctitis/proctosigmoiditis will usually be studied separately as local treatment forms the mainstay of treatment for these patients. Disease severity can be classified into 3 main categories, mild, moderate and severe UC (see 3.1.1). Inclusion of patients into Phase III trials should preferably be limited to only one of these categories. Alternatively 2 categories may be included (e.g. moderate to severe) but in that case the study should allow for separate estimation of effect size in both groups. Exceptions from this may be studies in steroid dependent patients where severity of the inflammation may not adequately reflect the severity of the disease and thus separate trials may be performed in this population, independently of the severity.

3.3.2.1 Choice of comparator

Choice of comparator will depend on the indication claimed (first line, second line or add-on) and the aim of the trial, induction of remission versus prevention of relapse, as well as the extent and severity

of the disease. The extent and severity of the disease will also influence the choice of formulation to be used (e.g. rectal in proctitis/procto-sigmoiditis, oral for more extensive disease and i.v. for severe colitis). The comparator can be placebo or active control.

Placebo control: For a first line indication, placebo controlled studies are not acceptable in moderate to severe active disease or for the prevention of relapse and should be justified in mild active disease. In both induction trials as well as maintenance studies, for a second line indication or add-on treatment, placebo would be acceptable.

Active control: The aim can be either to demonstrate superiority or non-inferiority to an active control. Choice of active control should reflect standard practices and approved indications for drugs on the market. For the design of non-inferiority trials, the delta should be clinically meaningful and pre-defined based on previous placebo controlled trials in a similar population and using similar definition of remission. The option of a 3-arm trial with placebo and an active comparator, where the latter would serve as an internal reference may be acceptable in certain circumstances, e.g. when the size of a non-inferiority trial is a problem. The choice of active control depends on the aim of the study, i.e. induction of remission versus maintenance of remission.

- Induction of remission: For mild and moderate active UC extending beyond the sigmoid colon, 5-ASA/sulfasalazine is the comparator of choice. For induction of remission in severe UC systemic corticosteroids should be used. For proctitis and procto-sigmoiditis topical treatment with either 5-ASA or corticosteroids may be used as active control. Double-dummy designs may be needed when the study formulation differs from the standard treatment formulation.
- Maintenance of remission: For maintenance studies, 5-ASA/sulfasalazine should be the comparator. In the refractory population (already receiving 5-ASA/salazopyrine), comparison with immunosuppressive agents (AZA/6-MP) is recommended, but placebo may be acceptable, see above on placebo as control.

Studies including “episodic re-treatment” should use same comparators for the treatment of a relapse as in induction studies.

3.3.2.2 Duration of studies

Studies for induction of remission: Duration of induction studies should be 8 to 12 weeks. The primary efficacy endpoint, remission rate, should be evaluated at 4 to 8 weeks. Once obtained remission should be maintained throughout the duration of the induction study. Earlier evaluations can be made for response e.g. after 2-4 weeks.

Studies for maintenance of remission: The duration of maintenance studies should be at least 1 year. A minimum of 12-week follow-up off treatment is recommended or alternatively a randomised withdrawal phase may be added.

3.3.2.3 Previous and concomitant treatment

Patients with UC usually receive maintenance treatment and should in general be allowed to continue with these during a trial in active disease as background therapy. The duration and dose of concomitant treatment prior to inclusion should be defined. For 5-ASA, a stable dose for > 2 weeks is appropriate for induction studies and > 4-6 weeks for maintenance studies. Treatment with AZA/6-MP requires stable doses for at least 3 months.

When concomitant treatment is not to be allowed, adequate wash-out period should be defined. For newer immunomodulating agents, the wash-out period may be uncertain but many have prolonged action. Adequate wash-out period based on the pharmacodynamic effect of these agents should be ensured.

For a refractory population, it should be ensured that patients have received optimal treatment before randomisation. A minimum duration and dose of previous (baseline) medication should be defined. For a second line indication in moderate and severe disease, corticosteroid use baseline is a requirement. History of previous use of corticosteroids and 5-ASA is of little relevance, as most patients diagnosed with UC will have used these medications at some time during the course of their disease. Such previous use should not be confounded with refractoriness. Corticosteroid dependency

should be defined as previously specified. Intolerance should also be defined by minimum criteria of severity, e.g. previous mild and resolved side effects to corticosteroids that did not lead to discontinuation of the treatment would not classify as patient being intolerant to corticosteroids. Refractoriness to AZA/6-MP requires at least 3-6 months of treatment without improvement.

Tapering schedules for glucocorticoids during trials should be standardised. Usually tapering can be done with 2, 5 to 5 mg/week in induction studies. Too rapid tapering is to be avoided. If bridging to AZA/6-MP is the purpose of the trial, the tapering of the investigational drug should be over 3 months at least.

Concomitant treatment with topical treatment in extensive disease may influence the endoscopic findings with sigmoidoscopy and thus it would be acceptable not to allow this kind of treatment. Antibiotics should normally be excluded and in severe disease, anti-cholinergic, anti-diarrhoeal, NSAID and opioid drugs should not be allowed as they may contribute to worsening of the relapse.

3.4. STUDIES IN SPECIAL POPULATIONS

3.4.1. Studies in elderly

Separate studies in the elderly are not needed. It should be ensured that adequate number of elderly patients and patients with long-standing disease are included in the trials.

3.4.2. Studies in children and adolescents

Notice should be taken of the NfG on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99).

The majority of paediatric patients are older children and adolescents. The disease is often more extensive and highly active in pre-pubertal children. Growth and nutrition may be affected.

Studies in children and adolescents are encouraged. For the youngest children, the development of a suitable formulation is encouraged as well. Appropriate lower age-limit for inclusion into paediatric trials would be from the age of 6-8. In the refractory paediatric population, steroid withdrawal (while maintaining remission) is an important outcome and would be acceptable as a primary endpoint. Measurements of growth, nutrition and pubertal development should be included in trials in children with UC. Extra-intestinal manifestations are more common in the paediatric population and response with regard to these is an important secondary endpoint in paediatric trials.

3.4.3. Studies in other sub-groups

Fulminant colitis

Patients with fulminant colitis form a small sub-group of patients with UC. Limited amount of data for this group of patients may be acceptable for this indication, but will need to be supported by other data, (in particular safety data, but also data on efficacy in other subgroups of UC and/or other diseases. Fulminant colitis may be defined using validated indices that predict colectomy in this population, e.g. the fulminant colitis index and the Oxford criteria. Evaluations should initially be on a daily basis. Studies should be either active controlled (standard care including high dose corticosteroids) or placebo-controlled add-on to standard care. Avoidance of colectomy short-term and long-term is relevant primary endpoints in this population.

Pouchitis

Patients with pouchitis post-colectomy with ileal-pouch anal anastomosis form an important sub-group of patients with UC. Design should be double-blind, randomised, controlled trial. The management of pouchitis aims at reducing bacterial overgrowth and inflammation but resistance to medical therapy is reported in up to 20%. Antibiotics form the mainstay of treatment and can be used as control in studies with new medicinal products in pouchitis. For acute pouchitis (< 4 weeks), metronidazole or ciprofloxacin should be used as comparators. In chronic pouchitis placebo control is acceptable. The diagnosis should be confirmed by endoscopy and histology. The 18-point Pouchitis disease activity index (PDAI) can be used to measure disease activity and response.

Extra-intestinal manifestations

Extra-intestinal manifestations occur in a sub-group of patients with UC. They can be classified into “reactive” symptoms associated with active colitis and manifestations that occur independently of the

inflammation (e.g. ankylosing spondylitis and primary sclerosing cholangitis). Separate studies are not needed in this sub-group but response to treatment should be monitored in trials and analysed separately. Primary sclerosing cholangitis is a highly pre-malignant condition and special consideration should be given to this patient population when included in trials with new immunomodulating agents.

3.5. CLINICAL SAFETY EVALUATION

3.5.1. Specific adverse events to be monitored

All potential adverse events (AE) including those predicted by the pharmacodynamic properties of the investigational product should be collected and analysed using a pre-planned methodology. As for other medicinal products, AE need to be fully documented by system organ class.

For drugs with an immunomodulatory action, risk of neoplasia, infections and autoimmune disease is of particular interest.

Any groups at increased risk of AE should be identified. Depending on the indication, study endpoint(s), study duration, study population, as well as available knowledge about the safety of the drug, it may be relevant to establish a Data Monitoring Committee (DMC) to monitor safety data (please refer to NfG on Data Monitoring Committees (EMEA/CHMP/EWP5872/039)).

Depending on the product, an assessment of antibody formation, including evaluation of effects of antibodies on the safety and efficacy of the product, might be necessary. Consideration should also be given to the potential interference/contribution of concomitant therapy.

3.5.2. Duration of studies

As a major category of products used or tested in UC are considered to act as immunomodulators, special attention should be paid to autoimmune disorders and the tumour facilitating/inducing potential of these products. Further and full assessment of this effect could be done post marketing.

At the time of marketing authorization, it is expected that safety data of at least 1 year are available for a meaningful number of patients.

3.5.3. Interaction studies

Depending on the mechanism of action and based on the results of non-clinical data, Phase I and II trials possible safety concerns arising from PK or PD interactions with commonly co-prescribed medications should be investigated in Phase III studies.

Note: See <http://publications.eu.int/code/en/en-250304.htm> for guidance on referencing published information and <http://publications.eu.int/code/en/en-130102.htm> for guidance on referencing EU texts. References to related guidelines should also be included.