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Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing

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Executive summary

This guideline intends to address the EU regulatory position in the main topics of clinical development of new medicinal products in the treatment of chronic constipation, opioid-induced constipation, and for the development of medicinal products intended for the cleansing of the bowels before medical procedures needing a “clean” bowel.

1. Introduction (background)

Chronic constipation

Constipation is considered to be one of the most frequent gastrointestinal disorders, the prevalence of which is estimated to be around 11-18% in the general community , both in adults and children, with wide variability, depending on the definition of the disease, gender, geographical area, race, and concomitant drug intake. Because of its high prevalence and chronicity, the disease is responsible for considerable health care utilisation and cost. It also relevantly negatively influences Quality of Life of those affected, and can be debilitating. Constipation more frequently affects women, older people, and patients with a low socioeconomic status.

Historically, constipation has been defined on the basis of reduced stool frequency. However, more recently, constipation is more specifically defined on the basis not only of infrequent stools, but additional symptoms, such as reduced stool consistency, straining at stool, and sense of incomplete bowel evacuation. The Rome III criteria for functional gastrointestinal disorders define functional constipation (in adults) as the presence of at least two of the following: Straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual manoeuvres to facilitate defecations (these have to be present for at least 25% of defecations), and fewer than three defecations per week. These criteria have to be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. Additionally, the diagnostic criteria include that loose stools may only rarely be present without the use of laxatives, and that there are insufficient criteria for irritable bowel syndrome.

Functional constipation is usually used synonymously with chronic constipation, although the latter also includes “organic” or “secondary” disease, such as endocrine, neurogenic and drug-induced constipation. Chronic constipation can also be divided based on the underlying pathophysiology i.e. slow-transit and normal transit constipation, the former of which has been associated with a reduction in colonic intrinsic nerves and interstitial cells of Cajal and would therefore not be classified as “functional”. However, according to the currently available evidence, this distinction appears to have limited relevance as regards treatment. In contrast to the unclear relevance of the latter distinction, a clear need to distinguish constipation from evacuation or “defaecatory” disorders has been identified.

The development of medicinal products influencing gut transit and defecation is one of the oldest principles of pharmacological treatment. Numerous products have been introduced into the market even at times before drug regulation laws came into force within Europe. Nevertheless, the requirements for drug approval in this setting have never been laid down before, and the analysis of the data in support of many commonly used substances in the field have revealed that there is only insufficient evidence available to adequately support efficacy and safety of many of these substances.

The problem of chronic constipation has been viewed as relating to lifestyle problems, such as overall intake of a sufficient amount of fluids, on intake of a sufficient proportion of nutrients containing non-fermentable fiber, and on the level of physical activity and exercise. Many of these previous convictions

– similar to the concept of chronic laxative use leading to abuse and aggravation of symptoms – have been challenged, and it is currently considered at least uncertain whether changes in these three areas do play a role in the management of patients. However, the controversy appears to be ongoing with newer data emerging.

Opioid induced constipation

During the last 15 years there has been a steep rise in the use of opiates and opioids for chronic pain conditions, including non-cancer related pain. This rise has been most prominent in the United States of America, however, is also involving European countries. The increased use of opioids has led to a relatively sharp increase in patients affected with opioid induced bowel dysfunction (OIBD) or opioid induced constipation (OIC). Whereas the former relates to a multitude of complaints throughout the gastrointestinal tract, the latter is restricted to complaints similar to those in chronic constipation. In addition, for OIC, usually, tolerance to treatment (with decreased constipating effects) does not develop over time. The increase in incidence of opioid-related bowel disease, has led to an increased interest to develop and make available adequate treatment options for patients affected from OIBD and/or OIC in order to overcome the perception of limited efficacy of available medications in this special subtype of secondary constipation.

Bowel cleansing

Traditionally, all laxatives have also been used as purgatives for the cleaning of the bowel before endoscopic examination, radiological procedures, and surgery. The underlying need for the treatment with these agents, is therefore distinct from the normal use of medicinal products and the indication of bowel cleansing is often subsidiary to the main purposes of such products.

Due to the fact that the ingestion of the required amounts of fluids can be unpleasant and may lead to nausea and vomiting, have the potential to cause acute changes in water-, electrolyte-, and acid-base-balance a justification, demonstration of “global” usefulness, or proof of clinical utility for the underlying purpose of the bowel cleansing is considered necessary (see Chapter 4.4.).

2. Scope

This Guideline is intended to assist applicants during the development of products for the treatment of Chronic Constipation and the related fields of “Opioid Induced Constipation” and for the development of purgatives for the cleansing of the bowels in relation to procedures needing a clean bowel.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and Part I and II of the Annex I to Directive 2001/83 as amended. Applicants should also refer to other relevant European and ICH guidelines (in their current version), particularly the following:

Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95)

Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96)

Reflection paper on the extrapolation of results from clinical studies conducted outside Europe to the EU-population (Draft; CHMP/EWP/692702/08)

Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CHMP/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)

Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev 1)

Concept paper on the need to revise the guideline on the clinical development of fixed dose combinations of medicinal products regarding dossier content requirements EMA/CHMP/779887/2012.

Choice of Control Group in Clinical Trials (ICH E10, CPMP/ICH/364/96)

Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available (EMA/759784/2010).

4. Disease classification / possible claims

4.1. Chronic constipation

As mentioned above, chronic constipation can be divided into “normal transit constipation” and “slow transit constipation” although both of them are considered to be treated in a similar way. While “slow transit constipation” is associated with certain objective alterations after histological examination, both are usually summarised as “chronic functional constipation” or “chronic idiopathic constipation”. Both should clearly be discriminated from anorectal defecation disorders, but also from “secondary constipation” caused by other conditions , such as endocrine and metabolic diseases, medication (including opioids), or CNS (central nervous system) disease etc.

A treatment claim for chronic constipation should therefore in the future clearly be specified as “chronic functional constipation” or “chronic idiopathic constipation” (CIC), in order to state that secondary constipation has not been investigated for the compound.

A broad claim of “chronic constipation” is only possible, if relevant studies have also been conducted in secondary constipation.

4.2. Secondary constipation including Opioid induced constipation

Secondary constipation (due to underlying disease (e.g. endocrine or neurological) or medication) should usually be documented in separate studies in order to obtain a general constipation indication beyond idiopathic constipation only (see 4.1.). However, also broad studies including all types of patients could be regarded to be acceptable, if powered to show statistically significant effects in the subgroups.

Secondary constipation – as has been shown for opioid induced constipation – may be more difficult to treat, and extrapolation from a trial population in idiopathic constipation is not considered adequate. The intention to broaden an indication to “chronic constipation” (without the restriction to “idiopathic” or “functional”) would require the conduct of trials in both “disease models” for secondary constipation (a) due to underlying other diseases (e.g. Parkinson’s Disease, Multiple Sclerosis) and b) due to medication induced constipation (e.g. calcium antagonists, tricyclic antidepressants).

The choice of the claim – and hence the patients to be included into the development programme – will usually depend on the mode of action of the investigational compound.

A separate indication claim for secondary constipation, or even a part of secondary constipation (e.g. Parkinson's Disease related constipation) are considered to be unwarranted. It is expected that – apart from claiming chronic constipation without the suffix "idiopathic" or "functional" – data on secondary constipation could in general only lead to the inclusion of respective information in Chapter 5.1. of the SmPC.

The only secondary constipation entity for which a separate claim is considered adequate, is for "opioid induced constipation" (OIC). This indication can also be claimed if only opioid-induced constipation patients are investigated, especially where – as expected – the mechanism of action of compounds is the specific antagonist activity at the opioid receptor. A substance acting as an opioid antagonist would generally considered to be fully suitable for "opioid induced constipation" whereas a claim for the "general" secondary constipation indication would appear to be inappropriate.

The following chapters of this guideline therefore deal with development programmes for OIC only. Most of the recommendations given on development in OIC would, however, also be applicable to the conduct of studies in other fields of "secondary constipation", if it is indeed intended to broaden the general constipation indication.

A claim on "opioid induced bowel dysfunction" (OIBD) has to be separated from OIC, and would need the documentation of effects also relating to the upper gastrointestinal tract and/or effects other than on constipation and constipation related complaints alone. Constipation related complaints are defined similar to those included in the Rome III definitions. OIBD would however, also encompass reflux related complaints (heartburn, acid regurgitation), epigastric pain, nausea and vomiting, and biliary complaints including colic. This is considered to be outside the scope of this guideline.

4.3. Previous failed therapy

Previously failed therapy with other laxative compounds is a relatively common problem in day-to-day care of patients with constipation. Failing of therapy may theoretically be an even greater problem with patients suffering from secondary constipation, especially with OIC. A claim for the treatment of patients with previously failed therapy may therefore be desirable. However, any potential claim mentioning patients with "previously failed therapy" will have to be addressed specifically in clinical trials.

Simple history taking – asking patients whether they have indeed used other medicinal products in the past, and whether this has been unsuccessful – is not regarded to be sufficient in this regard. A claim of treatment of patients with "previously failed therapy on other ("usual") laxatives" will have to be substantiated. To this end, it is requested that patients with inadequate response to "usual laxatives" included into clinical trials will have to be adequately defined as follows: A patient with inadequate response to "usual laxatives" should confirm insufficient response to laxative treatment with at least two drug substances belonging to different classes used in the treatment of constipation (bulking agent/fibre, osmotic laxative, or stimulant laxative) by history taking. Additionally, the inadequate response to at least one of the agents should be documented during the run-in period of the trials.

If a general claim – without specifying the "line of therapy" is aimed at, the studies conducted should be powered such that a statistically significant effect is shown in both subgroups (first line and those with previously unsuccessful treatment).

4.4. Bowel cleansing

The use of purgatives – as mentioned above – before surgery and especially before colorectal surgery has been a matter of debate, in as it was not fully clear whether there is a clear patient benefit from the administration of such medication before the procedure. Whereas for colon cleansing before colonoscopy a clear dependence of the detection rate of colon adenoma on the quality of the bowel preparation has been found , the need for bowel preparation before surgery, especially before elective colorectal surgery has long been questioned. The latest meta-analytic review – with two large trials published in 2007 – finally concluded that mechanical bowel preparation did not reduce any postoperative complications.

Treatment claims for bowel cleansing agents should therefore – as a rule – be related to the treatment of patient scheduled for colonoscopy. Any deviating indication – relating to other diagnostic or to therapeutic procedures, including surgery, would need additional justification.

4.5. Potential targets of treatment

A wide variety of medicinal products is currently available on the market for the treatment of constipation. The available laxatives have been divided into fibre/bulking agents, osmotic laxatives (including undigestible disaccharides, Polyethylene-glycol (PEG), and salinic laxatives), and stimulant laxatives (such as diphenylmethan derivatives and anthraquinones). Despite the diversity of substances available, there is lack of effectiveness in a proportion of patients, which leads to relatively widespread patient dissatisfaction. The development of new compounds in this area is therefore ongoing.

Compounds that are currently under development include substances acting on the 5-HT4 (serotonine) receptor and compounds that stimulate secretion of fluid and electrolytes by various mechanisms, such as CFTR (Cystic fibrosis transmembrance conductance) channel stimulation, GC-C (guanylate cyclate C) receptor agonism, or inhibition of the ileal bile acid transport. A further mechanism of action may be represented by the inhibition of the intestinal N-H antiport protein (NHE3).

Also, probiotics have been identified which potentially play a role in the normalisation of stool related complaints, including functional constipation. Although most of these products appear to be developed as food supplements only, they have the potential to be developed as medicinal products also. The recommendations of this guideline do similarly apply to these kind of products compared to chemically defined substances.

Opioid induced constipation is generally recommended to be treated with the available armamentarium of laxatives. However, the efficacy of these compounds has proved to be limited. Therefore, a need to develop more specific treatments has been recognized. Several compounds are currently under development for opioid-induced constipation, all of which are based on peripheral antagonism to the μ-opioid receptor, and some of which are already on the market.

5. Clinical Study Design

5.1. Patient selection

5.1.1. Chronic idiopathic constipation

Early development:

In the early development of potential drug candidates, the pharmacodynamics (PD) properties with regard to the influence of the compound on intestinal transit, stool frequency, and stool consistency should be evaluated in healthy volunteers and/or in patients. Whereas generally patients may be selected based on the Rome III criteria for chronic functional constipation, a subdivision for patients with slow and with normal transit constipation (Slow Transit Constipation and Normal Transit Constipation; STC and NTC) should be made. During this early development, it is also considered necessary to carefully diagnose patients with defecation disorders and test the compound for its effects in this patient population separately, or exclude them from these early studies. During this phase, a full diagnostic workup with transit testing balloon expulsion test, defecation imaging, manometry, and EMG is recommended (see Chapter 6.2).

Phase II and phase III trials:

The recruitment of large numbers of patients in the later development makes the differentiation of patients with STC or NTC with the necessary full diagnostic workup impractical and unnecessary., unless differential responses become evident during the early development programme. Inclusion of patients can be based on symptoms alone, however, so-called “red flags” should be excluded (new onset of symptoms, anaemia, rectal bleeding, positive faecal blood test, weight loss etc.)

A different approach, however, has to be taken on patients with suspected defecation disorders, which should not be included into clinical trials in this indication. For these patients, indeed a lower response to laxatives has been shown to be likely, and the treatment recommendations are indeed different. Proposals for avoiding the “contamination” of clinical trials with these patients have already been made.

The Rome III criteria for functional constipation are the following:

- A patient must fulfil 2 or more of the following criteria:
  - Straining during at least 25% of defecations
  - Lumpy or hard stools in at least 25% of defecations
  - Sensation of incomplete evacuation for at least 25% of defecations
  - Sensation of anorectal obstruction/blockage for at least 25% of defecations
  - Manual manoeuvres to facilitate at least 25% of defecations (e.g. digital evaluation, support of the pelvic floor)
  - Fewer than 3 defecations per week
- Loose stools are rarely present without the use of laxatives
- There are insufficient criteria for irritable bowel syndrome (IBS).

Of these, several symptoms can also be considered to be present in defecation disorders. However, different to IBS, the Rome III criteria do not define defecation disorders on symptoms alone, but on a diagnostic workup including balloon expulsion test, defecation imaging, manometry, and EMG. Therefore, it is not sufficient to state that there should only be “insufficient criteria for defecation disorders”.

Because the sensitivity of digital rectal examination for the identification of dyssynergia has been reported to be quite satisfactory, it is recommended to include only those patients for which an increased sphincter tone has been excluded by digital rectal examination. Also, the suggested measures to exclude patients with high straining severity, and those that fulfil the Rome III chronic constipation criteria only with the use of the “25% manual manoeuvres” criterion should be applied. Therefore, the following in- and exclusion criteria should be applied:

a) A patient must fulfil 2 or more of the following 3 criteria:
   - Straining during at least 25% of defecations but severity should be less than 3 or 4 on a 5-point scale
   - Lumpy or hard stools in at least 25% of defecations
   - fewer than 3 defecations per week

b) A patient must fulfil all of the following:
   - Loose stools are rarely present without the use of laxatives
   - Normal rectal sphincter tonus on digital rectal examination
   - There are insufficient criteria for IBS.
   - No other reasons for constipation can be identified (e.g. medication).

c) A patient may suffer from the following additional symptoms:
   - Sensation of incomplete evacuation for at least 25% of defecations
   - Sensation of anorectal obstruction/blockage for at least 25% of defecations
   - Manual manoeuvres to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor)

These criteria should be fulfilled at recruitment (by history taking), and during the run-in phase of the studies (see Chapter 6.3). During the run-in period, the number of stools should not exceed 5 in two weeks.

For patients with idiopathic constipation, secondary causes for constipation should be excluded by appropriate history taking and assessment of concurrent symptomatology. Recent onset constipation should be checked for alarm symptoms and tested for stool blood.

Due to the ongoing debate about the clinical relevance of adequate fluid and fibre intake as well as adequate physical exercise as underlying cause and potential treatment for constipation, no strong recommendations can be given. However, all patients should be evaluated for grossly inadequate hydration, total absence of fibre-containing nutrients, and level of physical exercise. All patients should receive similar baseline recommendations and/or training regarding nutrition, fluid intake and exercise.

5.1.2. Opioid induced constipation (OIC)

Opioid induced constipation is considered to be very similar to chronic idiopathic constipation for its symptomatology regarding the lower abdomen and the bowel movement related complaints. The main feature of opioid induced constipation which has to be observed for clinical trial in this indication is the feature that the constipation has indeed been caused by the intake of opioids.

It is considered in principle acceptable that this can be done by simple history taking. Patients with opioid-induced constipation should have an intake of opioids of at least 3 months, and an onset of constipation after the start of opioid therapy. A certain threshold for the minimal daily dose of opioids should be applied and a stable dosing of opioids should be made a requirement for a certain period prior to inclusion into trials in patients with non-cancer pain (for cancer pain patients: see below). In this respect, a patient experiencing a severe aggravation of constipation symptoms after taking opioids could be regarded to be also suitable for investigation. However, due to the obvious difficulties in identifying an aggravation vs. a pre-existing disease, such patients are not recommended to be included in such trials.

Apart from the opioid induction of the constipation, the inclusion criteria for OIC should in other areas encompass the same criteria as for chronic idiopathic constipation.

Cancer-pain and non-cancer pain patients

Generally, it would be expected that for a full claim of the OIC indication, both, patients with non-malignant, as well as malignant pain are included into clinical trials. A different efficacy could be suspected – depending on the mode of action – for cancer patients, because they usually do receive higher doses of opioids and the condition might therefore be more difficult to treat. Because these patients suffer from more severe underlying conditions, it is considered necessary to separately document safety in these patients. There are also concerns that opioid treatment is often not stable in cancer patients as the disease progresses, and that their mechanism for constipation may be from other causes related to the malignancy and not just be from opioids.

However, the constipation caused by opioids is in principle not considered to be different for patients suffering from cancer-related pain or non-cancer related pain and extrapolation of data is at least partly considered appropriate. Therefore, the following requirements apply:

- If the main part of the evidence of a development programme is expected from trials in non-malignant pain patients:
- (An) additional safety trial(s) in the malignant pain population will be required for a full indication of OIC.
- The transfer of efficacy from non-cancer pain patients to cancer pain patients should be based on a sufficiently large subgroup from the studies in non-cancer pain patients, who are treated with high doses of opioids.
- If a sufficient number of high-dose patients has not been included in these studies, additional short-term efficacy studies should be conducted.
- If the main (or primary) part of the evidence of a development programme is expected from trials in cancer pain patients:
- In this case, due to the differences in the definition of the patient population (see below) a “full extrapolation” of efficacy will not be acceptable. This relates mainly to the restricted possibilities of patient recruitment in cancer-pain patients, and the need to show “sustained” efficacy and long-

term safety in the non-cancer pain population. (An) additional study(dies) will therefore be necessary in non-cancer pain OIC-patients.

Studies in cancer pain patients:

Patients entering studies in OIC with malignant pain should have a diagnosis of confirmed neoplasm, but with a life expectancy of at least 3 months.

Because the conduct of trials in the cancer-pain patients may be hampered by a grossly reduced willingness of investigators and patients alike to enter into studies that are only dealing with problems of supportive care and which might prevent them from undertaking all efforts to receive the optimal treatment for the underlying disease certain restrictions applicable to non-cancer pain patients should not be applied:

- The requirement of a stable dosing (prior to and during a clinical trial) can in most cases only partly be achieved for these patients and therefore, a more flexible approach is acceptable.
- For recruitment, a broad range of performance status can be applicable as long as the criterion for the life expectancy is fulfilled (see also Chapter 6.3 on study design and endpoints).
- The inclusion criteria may need to be simplified.

5.1.3. Bowel cleansing

Patients entering studies on bowel cleansing before diagnostic procedures requiring a clean bowel (usually colonoscopy) have traditionally been otherwise healthy subjects excluding relevant underlying disease. There are also certain conditions, in which bowel preparation is usually considered to be contraindicated, such as obstruction, ileus, perforation, diverticulitis, and gastric paresis. However, with the exclusion of patients with relevant pathology from clinical trials (those with diverticular disease, (quiescent) inflammatory bowel disease, etc.), and patients with underlying other conditions, such as cardiovascular, renal, and/or hepatic disease it is usually difficult to conclude an overall safe use of these procedures in the subjects that need to undergo such examinations most frequently.

The inclusion of “consecutive patients scheduled for colonoscopy” as done in most trials in the past will also in the future be acceptable for inclusion. However, because colonoscopy (and other diagnostic procedures on the bowel) have to be performed in populations that are usually screened for bowel pathology, or are even suspected of pre-existing pathology, the results/outcome of the diagnostic evaluation – and thus the “underlying pathology” – in the patients included in such trials should in future be reported, in order to at least assess the safety of patients with bowel pathology in comparison to those without. For the inclusion of “at risk-patients”, see Chapter 8.

5.2. Pharmacodynamic evaluation of drug candidates in early development

5.2.1. Chronic idiopathic constipation and opioid induced constipation

The need for evaluating the pharmacodynamic properties of drug candidates is not considered principally different for substances proposed to treat secondary constipation, including antagonising the effects of opioids, compared to those intended for the treatment of idiopathic constipation. Essentially, all substances suitable to tackle “primary” constipation might also be suitable for secondary constipation. There are only the specific opioid-receptor (μ-receptor) antagonists, for which a claim for idiopathic constipation may not be considered to be suitable.

The measurement of gastrointestinal transit (and/or parts of total transit; usually colonic transit) should be done in healthy volunteers and in patients (separate for patients with STC and NTC). The method of choice appears to be the use of radiopaque markers for which a variety of methods are available. Alternatively radionuclides with gamma scintigraphy or wireless capsule methods (based on pH evaluation) or a combination of these may be used. During this part of the drug development, when the substance is tested for the first time in patients, a clear exclusion of patients suffering from defecations disorders is considered necessary (see Chapter 6.1.1.). The influence of the drug candidate on total gastrointestinal and/or colonic transit should be evaluated, and correlated to the observation of the symptoms (e.g. stool consistency, frequency, other sensations) and the evaluations of stool (e.g. stool weight, content in electrolytes etc.) because these do not “perfectly” correlate. In addition, a simultaneous recording of colonic pressure by barostat can be evaluated.

During these early trials, a differential effect regarding gender should also be adequately evaluated. Therefore, both men and women should be included already at this stage of development.

5.2.2. Bowel cleansing

The development of new substances for bowel cleansing, as well as the development of new combinations of known substances requires the conduct of several sophisticated methods to evaluate the influence of the purgative regimen on a variety of physiological functions. The focus in the early evaluation of these compounds is therefore not only on the effects on colonic transit, but more on the influence of the induction of diarrhoea by these compounds in a variety of physiologic functions.

The application of either a large amount of fluid to, or the production of such by the body itself in the bowels may theoretically have an influence on a variety of parameters, encompassing not only cardiovascular (blood pressure, heart beat frequency), and renal function (serum measurements, eGFR), as well as serum chemistry (electrolytes including magnesium, phosphorus and calcium, pH, and acid-base balance), and the composition of body fluids such as stool and urine (total amount/weight, osmolality, electrolyte content/composition, total net water balance).

A full monitoring of the total of these functions will be necessary during the early development of new purgative regimens.

During these early phases of development, different regimens as regards the timing of the intake can also be explored.

5.3. Interactions

If compounds – whether used for the treatment of constipation or for bowel cleansing – are systemically available and do exert their effects not or not only on the basis of osmotic effects (i.e. a receptor target is identified) the evaluation of interactions should be done similar to other compounds according to the respective guideline.

All substances, however, whether fulfilling the above criteria or not, will be subject to a suspicion of drug interactions due to their pharmacodynamic action, in as the influence on motility and secretion may also influence absorption of other compounds. Although the potential problem is largely unexplored and only a few data are available , this should in future be addressed in respective drug-drug interaction studies based on the mechanism of action of the compound, and potentially in in-vitro experiments which could help to determine adequate test substances. Oral contraceptives are regarded to represent a good example for a widely used compound to be tested.

5.4. Dose finding

Generally, for this part of the development, consideration should be given to the Guideline "Dose response Information to Support Drug Registration" (ICH E4, CPMP/ICH/378/95). A full exploration of the dose-response relationship is generally expected.

For compounds with a specific opioid-antagonising mechanism of action, this needs to include the exploration of the coverage of the full range of potential opioid-doses, and the answer to the question whether a specific ratio of the agonistic/antagonistic activity at the μ-opioid receptor, or a specific dose level ("one size fits all") confers optimal pharmacodynamics activity.

5.5. Combinations of active substances

Treatment of constipation is usually not performed with the combination of substances, even if a patient experiences an insufficient response to one of the treatments, and the treatment algorithms developed by different scientific societies are not uniform . However, the addition/concomitant administration of agents with different mechanisms of action is theoretically adequate to overcome efficacy limitations with mono-therapy, and hence the development of fixed-dose combination medicinal products may be adequate for the indication.

The combination of opioids with peripheral μ-receptor antagonists is also regarded to be a potential option for the development of fixed-dose medicinal products for the indication OIC.

For the development of fixed dose-combinations for chronic idiopathic constipation and for OIC, there is currently no specific recommendation with regard to the development of fixed-dose combination medicinal products that goes beyond what is requested in the general guidance on this topic (CHMP/EWP/240/95 Rev 1 and EMA/CHMP/779887/2012).

However, this is different for products used as purgatives. This field of drug development has seen the administration of combined substances as a general rule, with both "usual" justifications for combination – increasing efficacy or decreasing undesirable effects of the combination partner – being equally present and important.

Whereas the justification of a drug-drug combination has usually to be based on the confirmative part of drug development (proving that the combination has better efficacy or less undesirable effects than the single substances), it can be potentially acceptable that this is done only in early parts of the development for purgatives/substances for bowel cleansing. Similar to the development of the macrogol-containing purgatives, that have added electrolytes with the aim to minimise water and electrolyte net exchange, the aim to reduce potential adverse effects at the "microscopic level" (such as disturbances of water and electrolyte balance) may be adequate to justify the addition of substances meant to counteract the adverse effects in purgatives, and as such of the combination, at an early stage of development only. It may therefore suffice to present data on in-vitro and/or human pharmacodynamics and on safety related biomarkers (e.g. electrolytes) only. If such an approach for justification of the combination is chosen, it has to be supported with adequate argumentation in all cases.

5.6. Confirmatory Clinical Trials

5.6.1. General requirements

Chronic idiopathic constipation

Double-blind, parallel group clinical trials should be performed. The trials should be long enough to determine if any response will be sustained, and to cover a potential late drop-out. The duration of such studies is recommended to be at least 3 months. Depending on the mechanism and speed of onset of action, the study may need a duration of up to 6 months. After the initial treatment period, an additional study period of at least 4 weeks should be added evaluating withdrawal and/or rebound, which can be best addressed with a randomised withdrawal phase.

Other study designs and/or durations will have to be justified in terms of their ability to adequately assess long-term sustained efficacy, withdrawal, and rebound, as well as safety. Information on re-treatment/intermittent treatment would be regarded useful considering the "usual" use of laxative compounds in clinical practice.

As a general rule, the comparator which is required in such studies is placebo and the comparison to placebo will normally be sufficient to conclude on the overall benefit-risk- balance of a product.

However, consideration should be given to conducting at least one trial with the use of an additional active comparator, due to the wide availability of such compounds and their proven standard of care status, widespread use, and well-established safety. If an active comparator is included, depending on the choice of comparator and the nature of the investigational compound, it should be aimed at documenting non-inferiority to the active comparator in addition to the usual documentation of "assay sensitivity" showing a significant difference from placebo also for the active control. However, if superiority is the aim of the comparison to the active treatment, this is, of course, also acceptable.

If an approach documenting assay sensitivity, without confirmative documentation of non-inferiority is chosen, and especially if specific claims in relation to marketed products are intended, the focus of the evaluations should lie on the potential advantages of the investigational compound in other domains (e.g. documenting better safety, ease of administration or administration schedule).

All trials should include a run-in phase of at least 2 weeks, during which any previous active treatment is withdrawn, except a defined rescue medication, and the full compliance with the inclusion criteria is documented. In case non-response to "usual laxatives" is needed to be documented (see Chapter 4.3.), the active therapy with insufficient response, has, of course to be maintained during the run-in phase.

Similar to other functional diseases, symptoms in chronic idiopathic constipation are not continuous, but may have an undulating character for their occurrence, their frequency and their severity. In clinical practice, patients do frequently not take medication on a continuous basis, but instead commonly do so on an intermittent, or even "on demand" basis. The patient population not taking medication continuously may, however, differ with regard to frequency and severity of symptoms. Nevertheless, new substances on the market, investigated with trials in, and licensed for, a population with continuous symptoms and for continuous treatment, may later be used in different patient populations with different use. A need to plan further "scenarios" of use can be anticipated.

It is generally recommended to seek Scientific Advice if any of such additional "scenarios" are pursued.

Opioid induced constipation

In general, the design of trials for OIC should be similar to the one described above for chronic idiopathic constipation. However, this applies only for the case in which a company wants to investigate the efficacy and safety of a compound in a population with non-malignant pain treated with opioids in the first place. If (safety or efficacy) studies in patients with malignant underlying conditions are conducted, it is advisable to use a different design, in order to facilitate recruitment of the patients (in addition to the potential different features mentioned for patient selection; see also chapter 5.1.2).

These potential changes concern the following features of the study(ies):

- The run-in period may need to be shortened
- The withdrawal of the "usual" laxative medication may be skipped. In this case, an "add-on-setting" will be investigated.
- In case an efficacy study has to be conducted, the randomised treatment period may need to be shortened. However, it is considered that usually, an at least 4-week period may be needed to adequately assess efficacy and safety. The choice of an "add-on"-setting would also generate the need to conduct additional studies in this setting in the non-cancer pain population, if a full "unrestricted" indication is aimed at.

The appropriate comparator for studies in opioid induced constipation is considered to be placebo.

Bowel cleansing

Studies for bowel cleansing before colonoscopy are requested to be active controlled studies, because the administration of a "placebo regimen" is not possible or can ethically not be justified. Although blinding should be included into trial designs whenever possible, this may not be possible if, e.g. different amounts of fluids have to be given with certain regimens. The administration of "placebo-fluids" is not possible, and would certainly invalidate the results as regards safety and efficacy.

It is therefore considered necessary to conduct, randomised, controlled studies, in which the aim should be to demonstrate at least non-inferiority of the new substance/compound/regimen. In case a non-inferiority study is conducted the choice of the non-inferiority margin should not be based on the difference of (any) active bowel cleansing medication to placebo but on a clinically acceptable difference of the endpoint used. This could be justified on the theoretical assumption of missed pathology with a poor bowel preparation. In any case, the proposed non-inferiority margin should be clinically justified.

5.6.2. Endpoints

Chronic idiopathic constipation and opioid induced constipation

Traditionally, stemming from the previous view on constipation that a main feature of the disease is the reduced frequency of defecation, trials evaluating new substances for the disease have used the frequency of bowel movements and its change from baseline as the primary efficacy endpoint. Later, the total frequency was restricted to so called "spontaneous bowel movements" (SBMs), or "complete spontaneous bowel movements" (CSBMs).

However, as seen in the chapter on inclusion criteria, and the general characterisation of the disease, this somehow still reduces constipation to a mainly frequency related disorder. A comprehensive evaluation is "what really matters in constipation", and hence the draw-up of a fully validated patient-

reported outcome measure (PRO) in the disease is still absent. Attempts for partial validation of such scales have been made, but can currently not be recommended to be used as primary endpoints.

In the meantime, until such an instrument is available, the use of a primary endpoint based on CSBMs will be considered to be acceptable because it incorporates spontaneity (without intake of any "rescue" medication (or any other laxative, including enema or suppository) within 24 hours before the bowel movement), as well as completeness, of the bowel movement. The assessment of CSBM in comparison to SBM only, has repeatedly been proven to be possible as such, and may even be more sensitive to detect differences (between active and placebo, and between doses). For the primary evaluation, a responder analysis is recommended which takes into consideration a response defined as at least 3 CSBMs/week and at the same time an increase of at least 1 CSBM/week compared to the baseline period. The primary evaluation should be based on an overall 75% response rate related to the total duration of the study (in weeks), including "sustained response" defined as fulfilling these criteria for the last 4 weeks of treatment.

The use of other primary endpoints would need the presentation of a thorough justification which should include an argumentation based on available evidence/validation data.

In a situation when a fully validated PRO is not available for use as primary endpoint, the concordance of primary and secondary endpoints is regarded to be of utmost importance. Therefore, a comprehensive evaluation of secondary endpoints should be part of the trials. These may comprise the following:

- The evaluation of the frequency of CSBMs and SBMs (numerical evaluation)
- The evaluation of stool consistency (with the Bristo Stool Form Scale; BSFS)
- The evaluation of further symptoms such as straining, completeness of evacuations, sensations of anorectal blockage, pain and discomfort and manual manoeuvres (e.g. "ease of passage" on a 5-7-point Likert scale; dichotomous evaluation for manual moeuvres etc.).
- Partially validated scales that assess constipation symptoms (such as Bowel Function Index (BFI) (OIC only), Bowel Function-Diary (BF-diary) etc), PAC-SYM, etc,
- Global scales such as "Global Impression of Change" (PGIC), assessment of "satisfaction with bowel habits" etc.
- Measurements of Quality of Life on generic (e.g. SF-36; SF-12) as well as disease specific instruments (e.g. PAC-QOL).
- The use of rescue treatment.
- Time to first SBM or CSBM after the first administration.

Opioid induced constipation in cancer pain patients

In a situation when the conduct of efficacy study(ies) is considered necessary in OIC (see 5.1.2.), it is generally expected that recruitment may turn out to be difficult in cancer pain patients. Therefore, it is considered acceptable to base the primary evaluation of efficacy on a numerical scale, in order to avoid the reduction of power with the construction of responder analyses. Usually, a criterion based on bowel movement frequency – however, with additional features, such as spontaneity and completeness (CSBM), and potential additional other features such as normal consistency (BSFS 3-4) can be used, comparing the change from baseline to the end of treatment.

In this scenario, the concordance of primary and secondary endpoints is regarded to be of even higher importance than usual. Responder analyses should be presented as secondary evaluations and may help to assess clinical relevance although statistical significant differences in these analyses are not expected.

Bowel cleansing

The efficacy of bowel cleansing should be measured by evaluating the “cleanliness” of the whole colon. Previously, a variety of scoring methods have been used, which in the majority of cases have not been validated.

Adequate – at least partial – validation work seems to be available for the Boston Bowel Preparation Scale (BBPS), the Aronchick scale, the Ottawa scale, and the Harefield Cleansing Scale . The choice of the scale to be used as a primary endpoint should in all cases be justified and discussed, and the respective validation exercises be presented. Scales without respective validation will not be considered to be acceptable. Because usually these scales attribute different ordinal scales on the different segments of the colon, a segmental evaluation of the cleanliness of the bowel should be used as secondary evaluation.

Efficacy of bowel preparations should – as a secondary evaluation – also be assessed in terms of acceptability to the patients. This can be done by simple questions on global impression on taste, willingness for repeat administration, and surveys of palatability (e.g. in case fluids are administered). A secondary evaluation – outside of the tolerability evaluations – is also the completeness of the intake. Further secondary endpoints may include insertion and withdrawal as well as total colonoscopy time, and the adenoma (or other irregularity) detection rate.

6. Studies in Special patient groups

6.1. Children

Consideration is to be given to Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CHMP/ICH/2711/99).

6.1.1. Functional constipation

Constipation in childhood is considered to be a common condition, which accounts for 3% of all consultations of general paediatricians, and 25-30% of paediatric gastroenterologists. The prevalence of constipation in childhood varies with age. The peak incidence of childhood constipation is thought to occur around the time of toilet training (age 2-4 years). Whereas incidence is thought to be very low in the first year of life, prevalence rates rise with a peak in school-aged children, for which prevalence rates between 17 and 34% have been reported.

While organic causes for constipation are rare, and usually detected in early childhood, 95% of childhood constipation is thought to be “functional” on the basis of a learned behaviour of interruption of the defecation process with stool-withholding cycles leading to constipation, faecal impaction, and finally overflow faecal incontinence.

The definition of childhood functional constipation is based on the “Paris Consensus on Childhood Constipation Terminology (PACCT) Group, and the Rome III criteria , which include both the following:

Must include 2 or more of the following criteria for at least 2 months before diagnosis:

- Two or fewer defecation in the toilet per week
- At least one episode of faecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- presence of a large faecal mass in the rectum
- History of large diameter stools that may obstruct the toilet

The PACCT recommendations do not differentiate the age ranges, whereas the Rome III criteria give slightly modified criteria for infants/toddlers up to 4 years of age, which include a 1 months' time range before diagnosis only, incontinence episodes valid for children after acquisition of toileting skills only, and additional accompanying symptoms such as irritability, decreased appetite, and/or early satiety (which disappear following the passage of a large stool).

Due to the different underlying pathophysiology for most of the cases of childhood constipation, the conduct of separate trials in children is generally considered to be necessary. Separate dose-finding trials may also be necessary depending on the mechanism of action. For locally acting drugs, dose finding may especially be challenging. For the justification of the doses, animal or in-vitro models, as well as experience with established treatments may be used.

The inclusion of all age ranges (in sufficient numbers) between 0 and 18 years is considered to be necessary and clinical trials should usually be conducted double-blind and placebo-controlled. The inclusion criteria should fully reflect the Rome III/PACCT definitions.

Appropriate age ranges for which different trials need to be conducted (due to the need to use different endpoints and form of evaluation, see below) may concern the:

- Very young children before toileting skills are acquired
- Pre-school children
- School children (up to the age of 11)
- Older children and adolescents (12-17)

In situation in which anticipated recruitment problems might guide the selection of the age ranges and thus partial extrapolation and "interpolation" is aimed at, this should be justified based on the underlying pathyphysiology and the trials conducted.

Regarding the primary and secondary endpoints to be chosen for the proof of efficacy, the different age ranges may need to be evaluated in a different manner. However, the evaluation of stool frequency (as primary endpoint) and all symptoms according to the Rome III definition (if adequate for evaluation within the course of the trial; as secondary endpoints) should be part of the efficacy evaluations for all age ranges. For older school children and adolescents, some of the endpoint-recommendations as for adults are considered to be potentially applicable as additional secondary endpoints (measures of completeness, pain, or global scales). In younger children age-appropriate questionnaires may need to be developed (or administered if available). In young children below the age of 5, usually efficacy evaluation should be based on information received from the caregivers.

The duration of efficacy trials in the paediatric population can be 8 weeks only in cases where longer-term data are already available in adults.

About 50% of paediatric patients appear to recover within a period of 6-12 months. Therefore, to take full account of the patients not recovering and thus being in need for long-term therapy and to document long-term safety open-label extension trials should be conducted for a duration of 10 months (in order to make up for a 12 month overall duration of treatment).

6.1.2. Opioid induced constipation

The conduct of separate controlled studies in children is considered to be hardly feasible in this age range, because the incidence of the underlying conditions is much more rare in children. However, there exists an unmet medical need for those children that have indeed to be treated with opioids. Therefore, the conduct of studies for the determination of adequate dosing, and open-label studies to document adequate safety will be required in the paediatric population. Because principally the pathophysiology of the disease and the pharmacodynamics of opioid antagonising agents appear to be similar in children and adults, extrapolation of efficacy from adult data is considered adequate in these cases. For cases with a different mode of action, controlled data may be required.

6.1.3. Bowel cleansing

Diagnostic procedures requiring a clean bowel are also needed in children. Therefore, there is a need to develop age- and body-weight appropriate formulations and strengths for bowel cleansing. Depending on the nature of the treatment regimens, a full documentation of safety and efficacy is needed in the paediatric age range.

Trial designs should be adapted according to the specific clinical needs in the paediatric population with the use of general anaesthesia (and the consequent need for administration of the cleansing agent on the day before colonoscopy) and feeding tubes.

In case a new combination of well-known substances is proposed for a purgative regimen, it may, however, be possible to extrapolate efficacy and document open-label successful use and safety only. The extent of extrapolation will have to be justified.

6.2. Older people

Chronic functional constipation represents a considerable health care problem. However, it is currently not fully clear whether the prevalence for constipation is increased in the older people, but it is considered at least as high as in younger and middle-aged adults. It has been postulated that the prevalence is increased in the institutionalised population, however. Older people are also required to undergo colonic screening procedures more often than patients under the age of 60. Also, there is at least a theoretical potential for higher vulnerability of the adverse effects of laxatives in the elderly population. Moreover, older people do more frequently receive a variety of concomitant medication.

The recruitment of older patients – those above 65 and/or those above 75 – is therefore considered desirable for all studies included in this guideline at rates that are at least representative of the natural age range distribution. In phase III trials, therefore at least rates of recruitment that are informative about activity and safety in those aged above 65 will be necessary.

Depending on the theoretical safety risks and the safety results in early development of a compound or a treatment regimen, special safety studies in even more vulnerable populations are recommended (e.g. institutionalised/frail older people). Studies in frail institutionalised older people could account for

any deficiencies with the “regular” recruitment of a primary care constipation population that is in their majority consisting of middle aged women.

6.3. Gender

Chronic idiopathic constipation

On the basis of 26 studies, it has been estimated that the prevalence of constipation is about two times higher in women than in men. Usually, however, previous trials in chronic idiopathic constipation have recruited in their majority a predominantly female population of more than 80%. In the future, trials should aim at recruiting at least about 30% of their patient population from the male gender, in order to be representative.

Gender differences should also be evaluated during early development of a compound, and if differences are found, a separate programme for male and female patients (e.g. with different doses) may be necessary. If a relevant difference is not expected, nevertheless, the population should be stratified according to sex.

An omission of either male or female patients from the development is not considered to be desirable, unless clearly justified by grossly reduced expectance of efficacy, or grossly increased potential risks.

Opioid induced constipation and bowel cleansing

Both genders should be adequately represented in the trials as discussed above regarding chronic idiopathic constipation.

6.4. Geographic region

For “global developments”, recruiting patients from several regions of the world, the inclusion of a sufficient proportion of patients recruited in Europe is recommended unless it can be demonstrated that this is not necessary. This justification should be based on the analysis of ethnic/geographic and cultural factors according to the requirements of the respective guidance documents (ICH E 5, EMA/CHMP/EWP/692792/2008) should be presented at the time of MAA.

Previously, however, a relevant part of development programmes have focussed in their development on the United States or North America, and aim or aimed at inclusion of a North American population only.

In general for the condition chronic idiopathic constipation and for bowel cleansing, but depending on the mode of action of certain compounds and assuming that a population with mainly European descent is included, the transfer of data from the North American to a European population appears to be possible.

This is considered to be different for the condition of opioid-induced constipation for patients recruited in the US. Prescribing of opioids – especially for non-malignant diseases – is considered to vary widely between the US and Europe. Patients appear to receive opioids for largely different indications and for milder underlying (pain) conditions than patients in Europe. Because a population affected by more severe underlying conditions may have a relevantly different safety profile, the inclusion of a relevant proportion of patients recruited in Europe – or from regions with comparable prescribing practice of opioids – is recommended in the indication OIC.

7. Safety

Chronic Idiopathic Constipation and Opioid Induced Constipation

Because chronic idiopathic constipation (as well as opioid-induced constipation) are non-life threatening conditions, and purgatives are usually administered to otherwise healthy people, the safety of any therapeutic intervention is considered paramount.

The treatment of CIC and OIC will require intermittent or continuous long-term use of medication, and it is therefore necessary to have long-term safety data with an observation period of at least 12 months available in adequate numbers to accurately assess the safety of a medicinal product. The Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety (CHMP/ICH/375/95) is considered to be fully applicable.

The main focus of the safety evaluations should be on the evaluation of gastrointestinal events, especially if these events are theoretically the consequence of the primary pharmacology of the new compound, which is usually to influence gastrointestinal motility and secretion/absorption, thus leading to different defecation frequency and stool consistency.

The evaluation of safety should therefore focus on the induction of diarrhoea and the consequences hereof, namely the loss/change in net water (dehydration), electrolytes, acid/base balance. Also potential consequences of water and electrolyte changes/loss like change in heart beat and blood pressure, as well as hypotension and syncope as special events, should be in the focus of the safety investigations.

The focus of the evaluations is, however, also dependant on the primary pharmacology of a compound including primary and secondary pharmacodynamics, and the pharmacokinetics including the level of systemic exposure.

The potential of laxative abuse – one of the oldest problems in healthcare – should be assessed based on the PD properties and the results of the safety evaluations during development. However, laxative abuse can hardly be addressed with safety studies before licensing. Therefore, laxative abuse should be part of the Risk Management Plan with appropriate observational studies to be proposed to be conducted post-licensing.

Opioid-induced constipation

Special emphasis in the treatment of opioid-induced constipation – especially if the pharmacological mechanism of action is targeted at the opioid receptors in the gastrointestinal tract – has to be paid on the induction of opioid withdrawal symptoms, and on the impact on pain symptoms reflecting a potential interaction of opioid antagonist on the central analgesic effect.

Subgroups according to the types of opioid treatment should be analysed.

Bowel cleansing

For purgatives - where the administration is usually only once for considerable periods of time - no long-term safety studies are necessary. However, the evaluation of safety parameters as mentioned above is considered to be of utmost importance.

Special emphasis should be paid to the inclusion of relevant theoretical risk populations, once the safe use in an “otherwise” healthy population has been established. Depending on the mode of action, this may include patients with hepatic and renal impairment, heart disease, and pre-defined bowel disease (e.g. IBD).