25 June 2015
EMA/CHMP/407380/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on ' Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing ' (EMA/CHMP/336243/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	IFAPP (International Federation of Associations of Pharmaceutical Physicians)
2	Dr. jr. Stefan Bonne`(Belgian Federal Agency for Medicines and Health Products
3	Medicines Evaluation Board; The Netherlands
4	Norgine Ltd
5	TMC Pharma Services Ltd and Salix Pharmaceuticals Inc.
6	Mundipharma

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	IFAPP. The comment was expressing full agreement	No changes necessary
2	Dr. Bonné/Belgian Agency. The comment was contributing valuable additions to the guideline text.	Partial agreement with the proposals.
3	MEB. The comments were contributing valuable additions to the guideline text.	Partial agreement with the proposals
4	Norgine Ltd.	Partial agreement with proposals.
5	TMC Pharma Services Ltd and Salix Pharmaceuticals Inc.	Comments not agreed with. No changes implemented
6	Mundipharma	Comments not agreed. Only minor changes implemented.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
319-329	2	Comment: It is questioned whether efficacy studies are needed in cancer pain patients for the sole reason that these patients, in general, receive higher doses of opioids. If the cause of constipation is not considered to be different in cancer and non-cancer pain patient groups, the efficacy could be investigated in the subgroup of non-cancer pain OIC patients that take high opioid doses and subsequently extrapolated to cancer pain patients. It might be necessary, however, to document safety separately in cancer pain patients, but a PASS might serve this purpose. Proposed change (if any):	Partly agreed. The notion that efficacy in cancer pain patients can be justified by documentation of efficacy in a sufficiently large population of non-cancer pain patients treated with high doses of opioids is now included in the GL. The conduct of a documentation of safety pre-approval is, however, still included. The following recommendations regarding the conduct of efficacy trials in the cancer-pain population is therefore only for the cases where as sufficiently large number of patient with high doses in the non-cancer pain population has not been documented, or in case a company has decided to investigate cancer pain patients in the first place.
321-323	2	Comment: Although this statement seems logical at first sight, in practice limited data from a recently evaluated product for treatment of OIC indicated the opposite can be true as well, i.e. the response rate in strong and high opioid users was higher than in low and weak opioid users. Proposed change (if any):	Partly agreed. Wording has been changed to “could be suspected”.
486-487	2	As mentioned also earlier in the guideline, a substantial volume of OIC patients may have responded inadequately to standard	Agreed. However, the advice to adequately power the studies has been inserted earlier in the text (after previous line 188) where the problem of “previous failed therapy” is dealt with in

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		laxativespreviously. It is suggested that in studies aiming at a first line indication in treatment of OIC, the subgroups of new, previously untreated patients and those with a recorded inadequate response to standard laxatives are both sufficiently powered to allow for the assessment of efficacy in those groups.	a more general way, because this might not only be applicable to OIC.
491-496	2	Comment: For clarity, all specific changes allowed in the setup of clinical trials in cancer pain patients, both OIC and CIC, must be grouped and presented in one list/table for clarity. See also e.g. lines 340-348 for additional modifications allowed in cancer pain trials. Proposed change (if any):	Not agreed. The lines 340-348 deal with patient selection for trials in general, and the lines 491-496 deal with the trial design of the phase III confirmatory trials. However, a reference to the other potential different features has been included.
564	2	Although this endpoint might yield information of interest to the first time users of the product, it should be noted that the clinical relevance of this endpoint with regard to the treatment of chronic OIC is very limited and should not be used to claim efficacy of the product in chronic treatment OIC. Usually this endpoint results in an overinterpretation of the chronic effect of treatment.	Comment agreed with. However, it is considered that changes are not necessary, because this endpoint is mentioned among many other potentially more clinically relevant endpoints and should be viewed as additional marker of activity of the compound.
566-568	2	See previous remarks on the extrapolation of data from non-cancer pain patients to cancer pain patients.	Agreed. Subsequent changes have been implemented.
572-574	2	It is irrelevant to report responder analyses (or any other result) as a primary or secondary endpoint an	Agreed. However, a full deletion is not considered appropriate. To round up the picture, responder analyses and

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		add clinical relevance to it, when a study is known to be underpowered for this particular endpoint. In this particular case, lowering the number of patients included in the study will substantially reduce power for responder analyses since the primary evaluation is allowed on a numerical scale, and therefore concordance of primary and secondary endpoints is likely to be compromised due to lack of power for the secondary endpoint(s).	their concordance with the primary evaluation can contribute to the overall picture. The reduction of power, and the high chance of failing statistical significance is a triviality.
700	2	For clarity subtitles should be added here also in the guideline, i.e. Chronic idiopathic constipation and bowel cleansing on the one hand and Opioid induced constipation on the other.	Not agreed. The chapter deals with a “mix” of the three potential indications.
749-752	2	It might be of interest to include an additional safety analysis of patients according to the type of opioid treatment they are subject to. This might reveal patterns of opioid-specific safety issues.	Agreed. A respective paragraph has been inserted.
	3	There is no section on dose finding in the GL and it is suggested to add such a section. For OIC, it is suggested to add that the dose-response relationship between the opioid-antagonist and the background opioid dose should be evaluated (e.g. in a PD study).	Agreed. There was a small section referring to ICH E4, CPMP/ICH/378/95 at the beginning of Chapter 5. However, this has been expanded now to include the requirement for OIC.
	3	The title only reflects constipation, but a substantial part of the Guideline regards to the development of	Agreed. Title of the guideline expanded.

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		bowel cleansing products. Bowel cleansing is not necessarily related to constipation, and neither could be considered as a treatment option of constipation. It is therefore proposed to include bowel cleansing in the title as well.	
	3	The list of references is extensive. It is kindly suggested to leave out opinion articles and articles on validation of scales, and to select key articles providing data from systemic reviews, epidemiological studies or RCT.	Partly agreed. The list of references has been shortened.
	3	Several abbreviations are not explained, it is kindly requested to add a list of abbreviations.	Not agreed. The number of abbreviations is not considered extensive. A check has been performed whether all abbreviations are explained when mentioned the first time. When missing, this has been included.
	3	It is understood from the guideline that, in principle, the OIC (opioid induced constipation) indication could be obtained for laxatives that have a general effect on bowel function -and could be used in all forms of constipation- as long as additional studies have been performed in subjects with OIC. Although it is considered relevant to obtain data in this special population for “general” acting laxatives, it is proposed that a specific OIC indication will be limited to opioid-antagonists. Pseudo-indications” for all kind of conditions -e.g. neurogenic (MS, Parkinson, spinal cord injury) endocrine (hypotheryroidy, diabetes),	Partially agreed only. It is agreed that an indication of secondary constipation alone (or even parts of secondary constipation) are undesirable. However, the broadening of the indication from CIC to chronic constipation in general is considered to be possible. Respective changes have been included. Also, a restriction of the OIC-indication to specific treatments (the µ-opioid antagonists) is not considered adequate. If relevant effects are shown for such treatments, the indication should also be granted for compounds with a different MoA.

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		medicine-induced (anticholinergics, antihypertensive, opioids etc.)-should be avoided, as there is an overlap in symptoms and treatment response in these groups. If studies are performed for non-specific laxatives in the OIC population, the data could be included in section 5.1 of the SPC, as this may be relevant for the patients and prescriber.	
	3	According to this GL, separate (short-term) confirmatory studies on efficacy must be performed in cancer patients, for an OIC indication. On one hand, it is understood that there may be differences in co-medication, food and fluid intake, and opioid dose between cancer/non-cancer patients. On the other hand, it is questioned whether separate confirmatory trials in both populations should be a strict requirement, as OIC in non-cancer patients is in concept not different from OIC in cancer patients. This is e.g. illustrated by Relistor®, where the effect size in non-cancer pain patients was actually lower than in cancer patients (EMEA/H/C/ 000870/ II/0030). Instead, it is proposed that the MAH should justify that the product is effective at opioid-dose levels that are used in cancer patients. This may be separate randomized studies in cancer patients, OR data from non-cancer patients using high opioid doses, completed with additional observational safety data in	Partially agreed. The conditions under which a separate documentation of efficacy would be necessary for cancer pain patients have been specified (See Chapter 5.1.2.)

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		cancer patients. This proposal would also be in line with earlier decisions of the CHMP regarding Moventig (naloxegol).	
	3	European data are required for the OIC indication. It is questioned whether this should be a strict requirement, considering that the MOA of opioids is similar globally. There may be differences between Europe and other continents between patients' characteristics and diagnoses where the opioids are prescribed for, but this is ultimately expected to have little impact on the study outcomes.	This is not agreed with. For the sake of safety documentation, the inclusion of European patients is considered necessary based on the different prescribing patterns, and a potentially "milder" diseased population of non-malignant pain patients in the US.
line 74-80 / line 459-60	3	Comment: In this section it is stated that there is little evidence of the effectiveness of established laxatives in the treatment of constipation. Nevertheless, it is recommended to include an active control in at least one of the confirmatory trials of idiopathic constipation (section 5, line 459-460). It is suggested to provide more guidance on the main aim of such a trial in this section, being either efficacy or maybe more likely for safety. Proposed change (if any):	The characterisation of the usual laxatives has been slightly expanded.
line 89-98	3	Comment: It may be added that at chronic use of opioids, no	Agreed. The lack of development of tolerance has been added.

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		tolerance develops for the opioid-induced constipation effects. Furthermore, OIC has always been a problem in the past, before increase of prescribing opioids in non-cancer pain. Proposed change (if any):	
line 145-149	3	Comment: It is stated that separate studies are needed to substantiate a claim in secondary constipation in two models: (a) disease related (e.g. Parkinson's Disease patients, MS), or (b) due to medication use (e.g. calcium antagonists and TCA). However, secondary constipation is a very heterogeneous group, and it may not be feasible to perform studies in the proposed models separately. An alternative approach may be to include a broad population in the study with both primary and secondary constipation, and to stratify the relevant subgroups at randomisation. This option may be added to line 146. Proposed change (if any):	Partially agreed. A potential claim for "secondary constipation" is now no longer included (and declared unwanted), and the recommendation to conduct separate studies is changed from "in all circumstances" to "usually". A possibility to include the secondary population as subgroups has also been added.
Line 226-36	3	Comment: It is stated that PD studies should be performed in both patients AND healthy volunteers. It is not understood what could be gained from healthy volunteers studies and why this is an absolute	Agreed

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		requirement. Proposed change (if any): Suggested to change into “patients AND OR healthy volunteers”.	
line 270	3	Comment: It is proposed that only patients are selected for the Phase 2-3 trials without increased sphincter tone (as measured by digital rectal examination), in order to exclude patients with dyssynergia. However, this is rarely done in clinical practice, and interpretation might still be rather subjective. Further, in the absence of increased sphincter tone there might still be an outlet obstruction. Therefore, it is recommended to delete absolute this requirement from the GL. Proposed change (if any):	Not agreed. This simple method has shown a high diagnostic accuracy in studies and is so easy to perform that it is considered most suitable for used in Phase II/III
Line 408-418	3	Comment: A faster transit thought the digestive tract may have consequences for the absorption and efficacy of e.g. anticonceptives and other critical drugs. It is proposed to add that these kinds of interactions should be addressed by the MAH. A bio-equivalence interaction with contraceptives may be mandatory considering the target population of often young women.	Agreed. This was in principle already included. The example contraceptives has been added.

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		Proposed change (if any):	
line 420-431	3	Comment: It is suggested to delete or shorten this section, and replace by a statement in Section 2 that fixed-dose combination are beyond the scope of this GL, since no specific guidance could be given beyond what is provided in the EMA Guideline on fixed-combinations. Proposed change (if any):	Not agreed. The paragraph on the purgatives is regarded to be deviating from the usual requirements.
Line 452	3	Comment: The duration of the trial is recommended to be at least 3 months. Given the long-term use, it is suggested to add a statement that longer follow-up in the controlled phase (e.g. 6 months) might be needed to demonstrate sustained efficacy. This may also depend on the onset of action. Information on re-treatment would be very useful (Line 475-82) given the potentially intermittent use. Proposed change (if any):	Partially agreed. However, a compulsory 6-month treatment requirement is hard to justify. The need to document re-treatment has also been added.
	3	Comment: The statement on assay sensitivity is not very clear and could lead to misunderstandings. It is recommended to reword line 461 – 465 as follows:	Not agreed. The intention was to recommend against a mere documentation of “assay sensitivity”, but to request for non-inferiority also, or for the documentation of other advantages if a 3-arm trial is performed. No changes implemented.

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		Proposed change (if any): If an active comparator is included, depending on the choice of comparator 461 and the nature of the investigational compound, it should be aimed at documenting non-inferiority 462 to the active comparator. However, if superiority is the aim of the comparison to the active 463 treatment, this is, of course, also acceptable. Simple documentation of superiority to placebo and 464 use of the active comparator for documenting “assay sensitivity” only, is not recommended. If an active comparator is included, either superiority against the active comparator should be shown or a placebo should be included. In both cases, assay sensitivity is guaranteed (e.g. separation from control can be assessed). In case of a trial with two active comparators without placebo, non-inferiority cannot be claimed due to lack of assay-sensitivity. Therefore a three-arm active and placebo controlled trial is recommended. If both active controls clearly separate from placebo, the constraints for formally showing non-inferiority are less stringent.	
Line 507-8	3	Comment: The statement that no active comparators are licensed for the OIC indication is not up-to-date, and could be deleted.	Agreed.

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		Proposed change (if any): The appropriate comparator for studies in opioid induced constipation is considered to be placebo, 506 because currently no clear treatment standard is available, and no license has been granted in the 507 indication.	
Line 536-7	3	Comment: The systemic development of such an instrument is therefore clearly warranted". A more neutral wording is preferred. The sentence could be left out the text, without loss of the context. Proposed change (if any):	Agreed.
Line 549	3	Comment: "In such a situation" A specification of which situation is meant, would be helpful. Proposed change (if any):	Agreed. Clarification added.
line 626-30	3	Comment: It is suggested to add some guidance and reflections on dose finding in the different age subsets /which may be quite a challenge for local acting drugs. Physiological models and experience with established treatments may be helpful in estimating the dose.	In principle agreed. However, due to lack of experience, no clear guidance can be given.

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		Proposed change (if any):	
Line 692	3	Comment: It is suggested to add that subjects should be stratified for age and gender in the confirmatory trials, since there may be differences in response. Proposed change (if any):	Agreed.
Line 752	3	Comment: A rewording is suggested as this is considered more clear `For theoretically compromising the efficacy of the pain medication´. May be replaced by `interaction of opioid antagonist on the warranted central analgesic effect of opioids should be evaluated `  Proposed change (if any): `For theoretically compromising the efficacy of the pain medication´. `interaction of opioid antagonist on the warranted central analgesic effect of opioids should be evaluated `	Agreed in principle. Slightly different wording included.
	4	Norgine believe it would be better to have a completely separate guideline for bowel cleansing agents. Bowel cleansing seems to be detached from the main topics in this guideline. A paragraph is added at the end of	Not agreed. It is acknowledged that bowel cleansing is a topic relevantly different from CIC and OIC. However, the similarities in compounds used, especially for the CIC indication gave the

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		each section, but in some cases unrelated to the constipation topic. Bowel cleansing is a large topic in itself and a separate guideline would allow for further specific and focused details to be included.	chance to generate the guidance at this point of time. The need for some guidance in the field also appears to be obvious. However, at the current point of time, a separate guidance was not felt appropriate.
4 - 5	4	Comment: Norgine recommend adding 'bowel cleansing' or 'bowel preparation' to the guideline title and that sections for each indication are clearly outlined. Proposed change (if any): Update guidelines as per comment	Agreed.
41 - 44	4	Comment: Norgine believe that it should be stated upfront that the guideline covers oral agents and agents administered per rectum. Proposed change (if any): Update guidelines as per comment	Not agreed. It potentially also covers agents with different mode of application (e.g. parenteral), at least for OIC.
100 - 101	4	Comment: Norgine suggest the addition of other reasons for bowel cleansing, e.g. prior to bowel radiological procedures, use in video capsule endoscopy (including 'booster' dose). Proposed change (if any):	Partially agreed. However, capsule endoscopy is considered to be included in the “neutral” term “endoscopic examination”.

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		Update guidelines as per comment	
101 - 103	4	Comment: Norgine suggest that this phrase/sentence is clarified as it is difficult to follow/understand. Proposed change (if any): Update guidelines as per comment to provide clarification	Agreed. Section reworded.
105	4	Comment: Norgine suggest replacing “is often” with “in some cases can be”. Proposed change (if any): Update guidelines as per comment	Agreed.
107	4	Comment: Norgine suggest replacing “clear immediate” with “perceived” and replace “come” with “be demonstrated”. Proposed change (if any): Update guidelines as per comment	Agreed.
197 - 200	4	Comment: Norgine would like to highlight that it should be noted that currently the only definitive way to measure the	Not agreed. The current proposals include the possibility of other indications, if an adequate justification is presented. A need

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		efficacy of a bowel cleansing agent is to examine the colon mucosa for cleanliness after the agent has been taken, and that the only way to examine the colon mucosa with sufficient scrutiny is via colonoscopy. However the proof of efficacy of a bowel cleansing agent to be used where the reason for wanting a clean bowel is, for example, surgery, a radiological procedure or videocapsule endoscopy (VCE), is difficult, as requiring patients in a clinical trial to undergo a colon cleanliness-assessing colonoscopy (to evaluate the effectiveness of the bowel cleanser) on top of the medically-required surgical, radiological or VCE procedure would be unethical, because of the invasive nature of colonoscopy and its attendant risks. Norgine would suggest that surgical, radiological or VCE procedures requiring bowel cleansing should be allowed to be included in the licence application for bowel cleansing agents and that the required justification for this need not include new/complete clinical trials but rather a rationale based on clinical practice. Proposed change (if any): N/A	for mentioning these other indications is not identified.
197 - 200	4	Comment: Norgine would like to highlight that it should be noted that currently the only definitive way to measure the	Not agreed. The current proposals include the possibility of other indications, if an adequate justification is presented. A need

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350 - 352	4	Comment: Norgine suggest the inclusion of screening and surveillance procedures to this sentence.	Not agreed. The purpose of the diagnostic procedure is not relevant for the intention of the statement.

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		Proposed change (if any): Update guidelines as per comment	
418	4	Comment: Norgine suggest replacing “potentially on in-vitro experiments” with “potentially in in-vitro experiments”. Proposed change (if any): Update guidelines as per comment	Agreed.
506 - 508	4	Comment: Norgine questions whether a current standard of care does not exist. Norgine suggest that opioid induced constipation is treated even if the intervention is not a pharmacological one. Treatment guidelines exist in the USA (http://www.guideline.gov/content.aspx?id=15434) Proposed change (if any): Update guidelines taking into consideration comment	Agreed. The paragraph has been simplified.
579 - 581	4	Comment: Norgine strongly suggest the inclusion of the Harefield Cleansing Scale as the initially cited validated bowel cleansing scale. The Harefield Cleansing Scale is designed to score each segment of the bowel with a score of 0 to 4. The overall success is associated with a grade, where grades A and B indicate successful bowel	Agreed. Harefield Index has been added. The need to justify and discuss the validity of the scale chosen is already included.

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		cleansing, and C and D indicate a failure of cleansing. Use of the validated Harefield Cleansing Scale ensures that, should there be poor cleansing in any segment, this will result in an overall “fail” grade. This approach is vital to prevent missed diagnoses from non-visualization of any part of the colonic mucosa wherein lesions may actually exist. This scale shows benefit over other scales as the other scales do not provide this high level of reassurance of cleansing on a segmental level. Norgine confirm that Harefield Cleansing Scale was used in the clinical trials of the approved bowel preparation product MOVIPREP® albeit that for some of these studies this was prior to its official validation and naming as the Harefield Cleansing Scale. Studies conducted using the Harefield Cleansing Scale include: • Phase II study NRL994-02-2004 (Worthington J et al. A randomised controlled trial of a new 2 litre polyethylene glycol solution versus sodium picosulphate + magnesium citrate solution for bowel cleansing prior to colonoscopy. Curr Med Res Opin 2008;24:481-8) • Phase III study NRL994-01/2001 (Ell C et al. Randomized Trial of Low-Volume PEG Solution Versus Standard PEG + Electrolytes for Bowel Cleansing Before Colonoscopy. Am J Gastroenterol 2008;103: 883-93) • Phase III study NRL994-02/2001 (Bitoun A et	

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		al. Results of a prospective randomised multicentre controlled trial comparing a new 2-L ascorbic acid plus polyethylene glycol and electrolyte solution vs. sodium phosphate solution in patients undergoing elective colonoscopy. Aliment Pharmacol Ther 2006;24:1631-42) • Phase III study NRL994-01/2004 (Ell C et al. Randomised, controlled trial of 2L PEG + ascorbate components versus sodium phosphate for bowel cleansing prior to colonoscopy for cancer screening. Curr Med Res Opin 2014, Ahead of Print), • Phase IV study NRL994-02/2006 (Ponchon T et al. A low-volume polyethylene glycol plus ascorbate solution for bowel cleansing prior to colonoscopy: the NORMO randomised clinical trial. Dig Liver Dis 2013;45:820-6) • Phase IV study NOR-01/2011 (PDR) (Pohl et al. Impact of the quality of bowel cleansing on the efficacy of colonic cancer screening: a prospective, randomized, blinded study. Manuscript submitted for publication). Additionally, new data utilising the Harefield Cleansing Scale will be presented at two international congresses during 2014:	

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		• Belsey J et al. Comparison of Harefield Cleansing Scale (HCS) and Boston Bowel Preparation Scale (BBPS) for assessment of cleansing prior to colonoscopy: an analysis based on 1865 patients in six clinical trials. • To be presented at the annual scientific meeting of the American College of Gastroenterology (ACG), 2014, Philadelphia, PA, USA (Poster number P329; http://acgmeetings.gi.org/pdfs/ACG14_Prelim_Program.pdf); and Halphen M et al. Pharmacodynamic and clinical evaluation of low-volume polyethylene glycol (PEG)-based bowel cleansing solutions (NER1006) using split dosing in healthy and screening colonoscopy subjects. • To be presented at the annual meeting of United European Gastroenterology Week 2014, Vienna, Austria (Poster number P0741; https://uegw.congress-online.com/guest/sciprg.menu) and at ACG 2014 (Poster number P330; http://acgmeetings.gi.org/pdfs/ACG14_Prelim_Program.pdf). It has been stated by the FDA that the scale used for	

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		MOVIPREP® (i.e. the Harefield Cleansing Scale) is regarded as a more objective scale (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022372Orig1s000MedR.pdf , pg 27) Norgine also believe there should be mention about careful selection of scale for use, as some define a level of acceptability at which some amount of the colon may not be adequately visualised, leaving lesions undetected (Halphen M et al. Validation of the Harefield Cleansing Scale: a tool for the evaluation of bowel cleansing quality in both research and clinical practice. Gastrointestinal Endoscopy. 2013:78(1):121-131) See attached reference. Proposed change (if any): Update guidelines as per comment	
583 - 585	4	Comment: Norgine believe that it should be stated more strongly that it is necessary to go to the segmental level to get a high assurance of visualisation of the colon, to see more discreet lesions e.g., flat lesions. The Harefield cleansing scale provides a high level of reassurance of cleansing on a segmental level. It provides the greatest degree of granularity, and thus rigour, at the segmental level –the colon is divided into five segments for evaluation of cleansing. Other scales	Agreed. “Can” has been replaced by “should”.

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		that consider cleansing at the segmental level, only divide the colon into three segments. Proposed change (if any): Update guidelines as per comment	
589 - 591	4	Comment: Norgine would like to point out that in a clinical trial situation, if compliance isn't encouraged to be high, this leads to an unreliable evaluation of cleansing efficacy. Proposed change (if any): N/A	No change proposed. The comment is noted.
592 - 595	4	Comment: This paragraph is unclear to Norgine. It is believed it's referring to those at lines 525, 565 and 575 of the document, but this sentence appears to sit within the Bowel Cleansing section. Proposed change (if any): Update guidelines to provide clarification	Agreed. The paragraph was intended to relate to CIC, OIC and bowel cleansing indications.
658 - 659	4	Comment: Norgine suggest the alternative option for formulation development should be on a 'body weight-appropriate' basis which may be more appropriate than an age-	Agreed. This appears to relate to appropriate strengths, which is therefore added also.

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		appropriate formation for bowel cleansing products. Proposed change (if any): Update guidelines as per comment	
666	4	Comment: Norgine suggest removal of the word “partly” from this sentence. Proposed change (if any): Update guidelines as per comment	Agreed. Whereas it is not disputed that even full extrapolation may be possible, a need for justification of the extent of extrapolation has been added for clarification.
667	4	Comment: Norgine suggest that it may also be possible to extrapolate pharmacokinetic data from adults using the appropriate models, literature and justification to support. Conducting pharmacokinetic sampling (e.g. blood, urine etc.) in the paediatric population can in some cases be unethical. Proposed change (if any): Update guidelines as per comment	Not agreed. Currently there is no reflection of PK documentation included. No issues have been identified that go beyond the “general” rules for PK documentation in the paediatric population. Therefore, the need to include statements on extrapolation is not accepted.
722	4	Comment: Norgine recommend these headings be written in full for clarification. Proposed change (if any):	Agreed.

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		Update guidelines as per comment	
Lines 218-222	5	Comment: Relistor® (methylnaltrexone bromide) subcutaneous injection should be acknowledged as an available treatment for opioid-induced constipation in patients with advanced illness since it was approved via the EU centralized procedure on July 2, 2008. Proposed change (if any): Additional statement starting on Line 222: "Relistor® (methylnaltrexone bromide) subcutaneous injection, a peripheral μ-opioid receptor antagonist, is approved via the EU centralized procedure for the treatment of opioid-induced constipation in advanced illness adult patients, aged 18 years and older, who are receiving palliative care when response to usual laxative therapy has not been sufficient."	Principally agreed. Relistor is on the market since 2008, and Naloxegol has received a positive opinion in Spetember 2014 (and is expected to be approved by the European Comission in December 2014. However, the wording is far too extensive and therefore not accepted.
Line 97	5	Comment: The limitations of existing therapies could be put in better context for explaining the need for improved and targeted therapies for opioid-induced constipation (OIC). Sponsor Rationale There is a significant unmet need for effective treatments for OIC in patients taking opioids for	Not agreed. The evidence for the insuffient response to "usual laxatives" is similarly weak than the overall evidence for their efficacy. Assumptions on the mechanism of action appear to be speculative only, and should therefore also not be included. The intention of the guideline is to leave the possibility to develop other compounds than μ-opioid-receptor antagonists for OIC also (although the likelihood of success appears to be indeed higher for the specific compounds).

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		chronic pain. OIC is a serious and often intolerable side effect of opioid therapy. Over-the-counter laxatives and other currently available treatments are often ineffective. Patients who fail or cannot tolerate currently available therapies are faced with reducing or stopping their pain medication in order to have a bowel movement or continuing with the additional pain and discomfort associated with the constipation. Over-the-counter laxatives (e.g., bulk agents, stimulants, and osmotic agents) have been the most frequently used traditional therapies for OIC. However, over-the-counter laxatives work via mechanisms that are unrelated to the receptor-mediated effects of opioids (Goodman and Gilman 1996). Typical regimens combine multiple laxative types, but these are largely unsatisfactory in providing constipation relief to patients who must use high doses of opioids for adequate pain control, and although widely used, have not been shown to be effective in well-controlled trials for OIC. A Cochrane review failed to demonstrate benefit for laxatives in the treatment of OIC (Candy; Cochrane Database System Review 2011). In one study of laxative use in chronic pain patients on opioids, < 50% of those who required laxative therapy achieved a desired laxation response at least 50% of the time (Pappagallo; American Journal of Surgery 2001).	

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		In 2013, Amitiza (lubiprostone), a chloride channel activator, was approved in the U.S. for the treatment of OIC in adults with chronic NCP (Amitiza Prescribing Information). However, lubiprostone does not fully address the unmet need for OIC treatment in this population and does not target the underlying cause of OIC. The efficacy of lubiprostone was assessed in 3 clinical trials. In the first two trials, for which positive results were obtained, lubiprostone was only marginally effective in treating OIC versus placebo (treatment difference of ~ 8%). In the third study, a treatment benefit versus placebo was not demonstrated. In these studies, the effectiveness of lubiprostone in patients taking diphenylheptane opioids (e.g., methadone) was not established. Further, the studies indicated that lubiprostone's efficacy diminished with increasing opioid doses. The use of lubiprostone in some patients is also limited by nausea, which is the most common adverse effect reported in the Amitiza prescribing information. Proposed change (if any):	
Line 506	5	Comment: Placebo is an appropriate comparator for the short-term assessment of safety and efficacy (4 weeks or less). For drugs with targeted mechanisms (see	Not agreed. The studies with Naloxegol have shown to have 3 months durations with acceptable drop-out rates (16-19%; See: Chey WD et al: Naloxegol for opioid-induced constipation in

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		below), a 4-week placebo-controlled assessment is adequate to demonstrate efficacy. Sponsor Rationale Use of placebo for long-term assessment (> 4 weeks) of efficacy and safety is confounded by (1) high patient attrition rates associated with treating a symptomatic disease with placebo or ineffective/marginally effective treatments (e.g., laxatives and stool softeners), and (2) study bias that includes compromising the study blind due to the rapid onset/offset of laxation for targeted mechanisms. This can have a profound effect on dropout rates during long-term safety and efficacy studies. Proposed change (if any):	patients with noncacner pain. N Engl J Med 2014; 370: 2370-2387) , both for placebo and active. In the non-malignant pain population, there exists a clear need to show efficacy in controlled manner for at least 3 months due to the (theoretically) unrestricted treatment duration in this patient population.
Lines 544-548	5	Comment: Primary endpoints for trials in OIC should be based on a drug's mechanism of action, pharmacology, and physiochemical properties. Although the proposed primary endpoint in the Draft Guidance is appropriate for medications that would need to be taken daily and chronically based on mechanism of action, there are other drugs (like methlynaltrexone) that have a targeted (pharmacological and receptor-based) mechanism of action that treats the receptor-based side effect of constipation caused by opioid	Not agreed. The proposed endpoints are regarded to correlate to the pharmacodynamic activity of a compound only, but not to the well-being of the patient, or the relevant features of the underlying disease. It is considered that for a patient it does not matter whether laxation takes place immediately after drug administration or in a delayed manner only. Also, an influence on the associated symptoms would also not be covered by the proposal.

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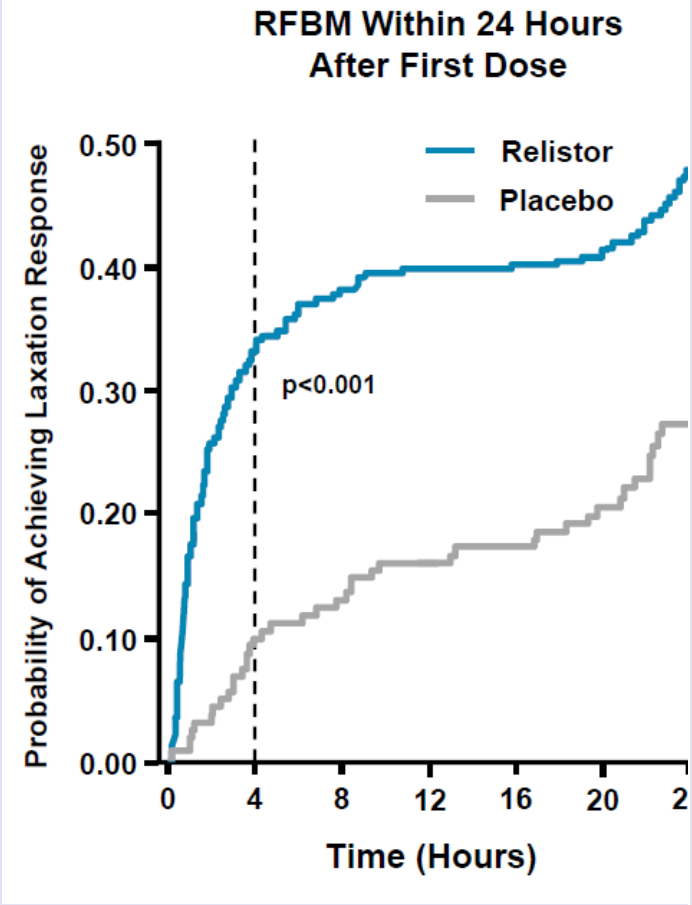
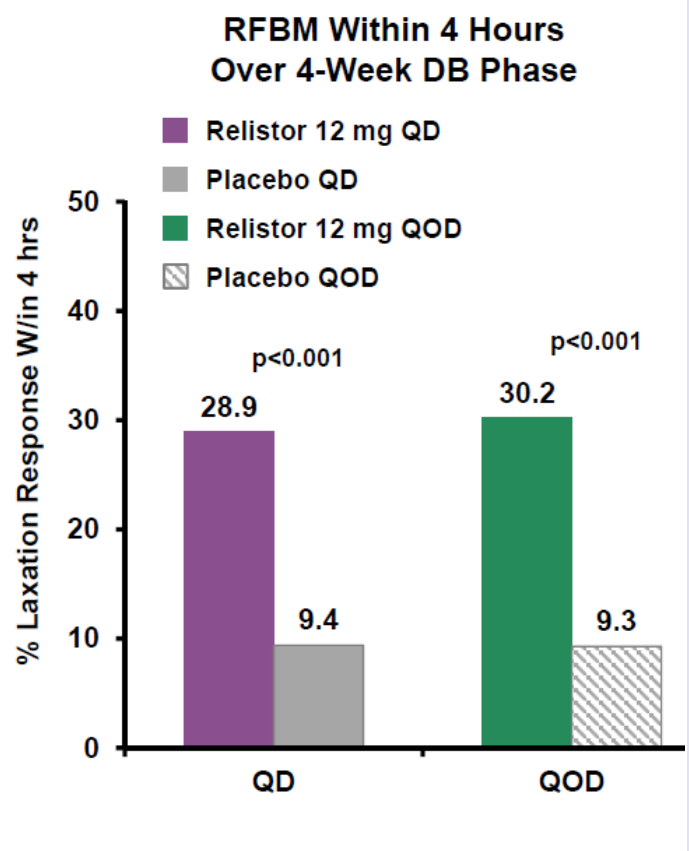
		administration. A primary endpoint of a “rescue-free bowel movement” within 4 hours of dose administration would provide both clinically meaningful and cost-effective benefits to a patient with OIC. 	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Figure 1: Relistor Study 3356: Rescue-Free Bowel Movement Within 24 Hours of First Dose  Figure 2: Relistor Study 3356: Rescue-Free Bowel Movements for Daily (QD) versus Every Other Day (QOD) Dosing	

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		For these reasons, primary endpoints should be based on the pharmacology, pharmacodynamics, and physiochemical properties of a drug; and how it would be used clinically (daily dosing or as needed dosing). As stated previously, this could allow labeling that is both clinically meaningful to the patient, and cost-effective to the healthcare system. Proposed change (if any):	
	6	OIBD is mentioned in early general sections, but later on, when it gets to the details of how to develop products, there is no mentioning of OIBD anymore...	A clarification has been added that the guideline is generally not dealing with OIBD as an indication. This explains why OIBD is not further mentioned. The guideline is written for an OIC indication only. Some hints, however, are given that clarify that the disease entity and hence the potential indication is different from OIC. No further changes necessary.
524ff	6	Comment: The Bowel Function Index (BFI) was developed to measure opioid induced constipation. The BFI is a clinician-administered tool and is based on a numeric analogue scale (NAS) of 0 to 100; 0 indicating freedom from symptoms and 100 indicating the most severe symptoms. The BFI is calculated as the mean of three variables: 1. ease of defecation, 2. feeling of incomplete bowel evacuation and 3. Personal judgment of constipation.. It is commonly acknowledged in the	Not agreed. The use of the BFI as primary endpoint, and an evaluation of the publicly available validation data had been done for the draft guideline already. It is acknowledged that the BFI has undergone valuable steps of validation, and may overall express the well-being of the patients. However, there are two unresolved problems with the BFI that stood against the choice/acceptance as primary endpoint:

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		scientific community, that opioid induced constipation is a syndrome which is mainly based on a subjective feeling of impairment of bowel function, as a pure measurement of surrogate parameters like bowel frequency are not sensitive enough to account for the interindividual differences of physiological bowel frequencies, from two bowel movements per week to two bowel movements per day still being seen as being in a physiological frequency range. Furthermore, pure frequency related parameters do not account for the important clinical symptom of straining or pressing, so the ease of defecation. The subjective parameter is essential for determining the clinical impact of opioid induced constipation. Patient reported outcomes like the BFI or the PAC Sym do account for the two main clinical symptoms described in literature, namely the ease/difficulty and completeness of defecation based on patients' subjective assessment of these relevant parameters. Using the BFI, patients rate these parameters according to their experiences in the preceding seven days. High BFI scores indicate poor bowel function and a change of greater than 12 BFI points can be viewed as clinically meaningful. The principle of using this rating scale provides patients and physicians with a familiar mode of assessment. It does not promote confusion or difficulty. However, The BFI has furthermore been	There appears to be a high risk of “recall bias” in as the symptoms are recorded once weekly only. This risk of recall bias has not been evaluated. The currently proposed primary evaluations (for both OIC and CIC) can easily be included into a patient diary and be recorded and evaluated on a daily basis, and would therefore cover day-to-day fluctuations of symptoms. Moreover, the questionnaire is not directly patient centered but filled in by the physician. It is unclear whether this also influences the results achieved with the questionnaire. However, the BFI is considered to be a valuable tool in the assessment of treatment effects in the disease and therefore explicitly mentioned as secondary efficacy variable. It must be acknowledged (and is included in the guideline) that there is currently no fully validated outcome measure. Hence a paragraph that does in principle allow the use of other primary endpoints with adequate justification and presentation of available validation data is additionally included.

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		validated against the PAC-SYM, and shows significant correlation with stool frequency, stool consistency and laxative-use in patients suffering from opioid induced constipation. Therefore, the BFI has been developed and validated specifically for OIC. An extensive analysis has been performed in order to validate the BFI as reliable, stable, clinically valid, and responsive to changes in patients with OIC. The results of the validation analysis were based on major clinical trials and have been further supported by data from a large open-label study and a pharmaco-epidemiological study, in which the BFI was used effectively to assess OIC in a large population of patients treated with opioids. Although other patient selfreport scales exist, the BFI offers several unique advantages. First, by being physician-administered, the BFI minimizes reading and comprehension difficulties; second, by offering general and open-ended questions which capture patient perspective, the BFI is likely to detect most patients suffering from OIC; third, by being short and easy-to-use, it places little burden on the patient, thereby increasing the likelihood of gathering accurate information. (Philippe Ducrotte Citation: Curr Med Res Opin 2012; 28:1–10) The validation programme did confirm that the BFI is a valid and reliable instrument for the assessment of opioid-induced constipation in chronic pain patients.	

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		Psychometric analyses from clinical trials support the BFI's psychometric properties. (A. M. Rentz1 Journal of Medical Economics, 2009; 12(4): 371–383). For the diagnosis and clinical aspects of opioid induced constipation, literature describes that validated instruments, such as the Bowel function Index (BFI) and the Patient Assessment on Constipation Symptoms (PAC-SYM) questionnaire, are helpful to assess the impairment in quality of life caused by OIC and may help to establish the indication for its treatment (Mueller-Lissner S, European Gastroenterology & Hepatology Review, 2010;6(1):54–7). In a cross sectional study by Ueberall, a reference range assessing BFI values in non-constipated pain patients was evaluated. The BFI values were compared to patients with confirmed opioid induced constipation from two previous separate studies. The results gathered demonstrated, that 95.5 % of pain patients without opioid induced constipation fell into a BFI range of 0-28.8, further delivering evidence for the differentiation of non- constipated and opioid induced constipated pain patients (Ueberall M.A., the Journal of internal Medical Research 2011; 39: 41-50). In conclusion, it is generally acknowledged that opioid induced constipation is a syndrome with a subjective clinical impairment of bowel function in patients. The BFI is a valid and reliable instrument to measure the	

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		symptom severity of opioid induced constipation, also defining responsiveness and indicates discrimination between opioid induced constipation and non-constipated status. The BFI furthermore demonstrated a high correlation to the PAC Sym, another validated PRO scale, measuring symptom severity of constipation, and also demonstrated consistent correlations to bowel frequency based parameters (CSBM), stool consistency (Bristol stool scale) and laxative use. Based on the aforementioned evidence of the validity of the BFI for measuring opioid induced constipation and the subjective clinical impact of opioid induced constipation based on patient report, we would suggest that the BFI should be considered as an alternative primary endpoint to the CSBM in clinical studies for assessing opioid induced constipation. The CSBM could in such cases be used as secondary endpoint to support the findings from the BFI. Proposed change (if any): Please add: The BFI should be considered as an alternative primary endpoint to the CSBM in clinical studies for assessing opioid induced constipation. The CSBM could in such cases be used as secondary endpoint to support the findings from the BFI.	