ITEM 5

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CENTRE FOR HEALTH TECHNOLOGY EVALUATION
Technology Appraisals

Consultation on Batch 29 draft remits and draft scopes and Summary of comments and discussions at scoping workshops

5.1	Lubiprostone for treating chronic idiopathic and opioid induced constipation
5.2	Alendronate, denosumab, risedronate, strontium ranelate, teriparatide, and zoledronic acid for the prevention of osteoporotic fractures in men
5.3	Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture

Provisional Title	Lubiprostone for treating chronic idiopathic and opioid induced constipation		
Topic Selection ID Number	6438	**Wave/Round**	R43
TA ID Number	647		
Manufacturer	Sucampo Pharma Europe		
Anticipated licensing information	**Chronic idiopathic constipation:** already holds a marketing authorisation for the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures are inappropriate. (Granted Sep 2012.) **Opioid induced constipation:** ***CONFIDENTIAL***		
Draft remit	To appraise the clinical and cost effectiveness of lubiprostone within its licensed indications for the treatment of chronic idiopathic and opioid induced constipation.		
Main points from consultation	Remit: The workshop attendees considered that as lubiprostone is already licensed in the UK for chronic idiopathic constipation and because it is a different condition to opioid-induced constipation, it would be appropriate to define 2 different remits. The workshop attendees highlighted that lubiprostone for treating opioid-induced constipation has only been studied in people with chronic, non-cancer pain. They therefore felt it appropriate to specify non-cancer in this remit. Comparators: 1. Chronic idiopathic The attendees noted that the licensed indication for lubiprostone for chronic idiopathic constipation does not restrict its use to patients in whom previous therapy with laxatives has failed, and therefore bulk-forming, osmotic and stimulant laxatives are appropriate comparators. It was noted that prucalopride is only licensed and recommended in women for whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered. Prucalopride would therefore be a relevant comparator for lubiprostone only for people for whom prucalopride is indicated. 2. Opioid induced: The workshop attendees agreed that bulk-forming, osmotic and stimulant laxatives would also be appropriate comparators in this indication. The workshop attendees noted that methylnaltrexone has only been studied as a treatment for opioid-induced bowel dysfunction in advanced illness or palliative care, and therefore, it was considered that it would not be an appropriate comparator for lubiprostone for treating opioid-induced constipation in people with chronic non-cancer pain. The workshop attendees also considered that prucalopride would not be an appropriate comparator for lubiprostone within this indication since it is only recommended for treating chronic constipation in women.		

	The workshop attendees agreed that faecal softeners, other agents used as prokinetics (such as erythromycin and gastrogaffin) and bowel surgery were not appropriate comparators for lubiprostone. The new suggested comparators are: - For people with chronic idiopathic constipation: o bulk-forming laxatives (ispaghula [psyllium] husk, methylcellulose, sterculia); o osmotic laxatives (lactulose, macrogol, magnesium hydroxide salts, phosphates, sodium citrate) o stimulant laxatives (bisacodyl, docusate, glycerol suppositories, senna, sodium picosulfate) o prucalopride for people for whom prucalopride is indicated - For people with opioid induced constipation: o bulk-forming laxatives (ispaghula [psyllium] husk, methylcellulose, sterculia); o osmotic laxatives (lactulose, macrogol, magnesium hydroxide, phosphates, sodium citrate) o stimulant laxatives (bisacodyl, docusate, glycerol suppositories, senna, sodium picosulfate) o rectal interventions e.g. suppositories and enemas Outcomes: Remove time to bowel movement - the time between the drug intake and the bowel movement does not adequately reflect the clinical effectiveness of the intervention. Add sense of complete evacuation – considered appropriate since it is part of the bowel function index. Remove response rate - not considered to be an appropriate outcome measure as it is already covered by frequency of spontaneous bowel movements. Remove pain - Pain was not considered to be an appropriate outcome measure. During consultation it was suggested to redefine pain as abdominal discomfort. However it was also noted that abdominal discomfort is already covered by symptoms of constipation. Therefore, it is suggested that pain is excluded as an outcome measure in the scope. STA/MTA: The indications refer to 2 distinct conditions for which the management of constipation is different. Therefore, it was suggested that it would be more appropriate to conduct 2 separate STAs. It was noted that there is a need for conducting a clinical

	guideline in the management of constipation (The scoping workshop report states that 'It was also agreed that NICE would inform DP4 of the need for a clinical guideline on constipation'). Some attendees also suggested conducting a MTA for all available interventions for the treatment of constipation because of the uncertainty around which interventions are most clinically and cost effective. It was asked during the scoping workshop whether it would be appropriate to conduct a MTA including a new drug (naloxegol) for treating opioid-induced constipation together with lubiprostone. Naloxegol does not yet have a UK marketing authorisation for treating opioid-induced constipation. It has been studied in clinical trials compared with placebo and usual care in adults with non-cancer pain and cancer pain and opioid-induced constipation, including those patients that have inadequate response to laxatives. The expected marketing authorisation timings for naloxegol are: ***CONFIDENTIAL*** Need for an appraisal: During consultation it was noted that there is an unmet medical need for treating both conditions and that there is urgency for producing guidance on both conditions.
Population size	Chronic idiopathic constipation: Reported prevalence rates of constipation in the UK vary widely between studies, with figures ranging from 4% to 20%. In 2010-11, there were 57,506 hospital admissions due to constipation in England. In 2010, there were 103 deaths registered in England and Wales due to constipation. Opioid-induced constipation: Approximately 32,000 people receive strong opioids (for cancer and non-cancer pain) in England for palliative care. Opioid-induced constipation is considered to be a side effect that will affect nearly all patients taking strong opioid treatment and that will persist unless treated.
Process (MTA/STA)	2 STAs
Proposed changes to remit (in bold)	• To appraise the clinical and cost effectiveness of lubiprostone within its licensed indication for treating chronic idiopathic constipation • To appraise the clinical and cost effectiveness of lubiprostone within its licensed indication for treating opioid induced constipation in people with chronic, **non-cancer** pain **(Separate the remits by the two indications)**
Costing implications of remit change	Costing comments were provided against two distinct STAs: 6438 – Lubiprostone (Amitiza) for chronic idiopathic constipation 6439 - Lubiprostone (Amitiza) for opioid-induced constipation in

	patients with chronic non-cancer pain The proposed changes in remit do not affect the costing comments already provided.
Timeliness statement	Chronic idiopathic constipation - Given that the technology has received its license in this indication, issuing timely guidance will not be possible. Opioid induced constipation - Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the expected referral date of this topic, issuing timely guidance for this technology will be possible.

Provisional Title	Alendronate, denosumab, risedronate, strontium ranelate, teriparatide, and zoledronic acid for the prevention of osteoporotic fractures in men		
Topic Selection ID Number	5629 (denosumab only)	**Wave/Round**	R19 (denosumab only)
TA ID Number	558		
Manufacturer	Alendronate – Accord, Merck Sharp & Dohme Denosumab – Amgen Risedronate - Warner Chilcott UK, Zentiva, Beacon, Sandoz Strontium ranelate – Servier Teriparatide – Eli Lilly Zoledronic Acid – Novartis, Teva, Hospira UK		
Licensing information	Only denosumab does not currently hold a marketing authorisation. Denosumab - ***CONFIDENTIAL*** N.b. Some technologies are licensed for men at 'increased risk of fracture', some for those at 'high risk of fracture' and some to 'prevent fracture'. The clinicians at the scoping workshop clarified that the different wording did not impact the use of the treatments as the marketing authorisations were perceived to be equivalent.		
Draft remit	To appraise the clinical and cost effectiveness of alendronate, denosumab, risedronate, strontium ranelate, teriparatide and zoledronic acid within their licensed indications for the prevention of osteoporotic fractures in men.		
Main points from consultation	Remit: Following the consultation exercise and the scoping workshop, the Institute is of the opinion that a referral for an appraisal of Osteoporosis (men) - Alendronate, denosumab, risedronate, strontium ranelate, teriparatide and zoledronic acid is appropriate. Population/subgroups: Clinicians stated that glucocorticosteroid use causes osteoporosis in men more than in women. It was therefore agreed that glucocorticosteroid induced osteoporosis should be specified in the population of the scope. Scoping workshop attendees agreed that both primary and secondary prevention should be considered within the same appraisal, but with primary and secondary prevention being addressed by the inclusion of 2 subgroups in the scope: people without a prior fracture and people with a prior fracture. Attendees at the scoping workshop discussed whether the population in the scope should include/exclude men who have bone loss as a result of androgen (hormone) ablation therapy. Clinicians explained that men who have received androgen ablation therapy have a higher risk of developing osteoporosis. They highlighted that treatments currently available for this population are often under prescribed in clinical practice. Attendees agreed that the population specified in the scope did		

	not require amendment but that a subgroup 'prior androgen ablation therapy' should be included.
	
	A number of other sub groups were raised during consultation. These were presence/absence of hypogonadism, alcohol intake (>4 units per day), and age (≥ 75 years). Attendees agreed that these sub groups should be included in the scope with the caveat 'should evidence be available'. Attendees noted that age was a risk factor for fragility fractures and agreed that subgroups by age range should be included in the scope.
	
	• The updated scope specifies the population as:
	  ○ Men with glucocorticosteroid induced osteoporosis
	  ○ Men with osteoporosis resulting from causes other than glucocorticosteroid use
	• The following subgroups have been added to the 'other considerations' section:
	  ○ People without a prior fracture
	  ○ People with a prior fracture
	• The following subgroups have been added to the 'other considerations' section; for consideration where evidence is available:
	  ○ People with risk factors for fracture (age, hypogonadism, alcohol intake, prior androgen ablation therapy)
	
	Comparators:
	Suggest that the comparators are updated to include 'no active treatment' and that each treatment is noted by name (rather than stating "to compare to each other").
	
	STA/MTA:
	Attendees at the scoping workshop agreed that the MTA process was appropriate and also indicated their support for an appraisal as soon as possible.

Population size	Approximately 3 million people in the UK are thought to have osteoporosis. It is estimated that osteoporosis affects 1 in 12 men over the age of 50. In 2009-2010, there were 3,957 hospital admissions for osteoporosis in men.
Process (MTA/STA)	MTA
Proposed changes to remit (in bold)	None
Costing implications of remit change	Original costing comments related purely to topic 5629 Denosumab for osteoporosis in men. The changes to the scope affect the costing comments. Revised comments are provided.

	It is estimated that osteoporosis affects 1 in 12 men over the age of 50, around 680,000 men in England. The cost impact of the topic using the new scope can't be estimated from the early data available. However, there are many factors that may influence the cost impact. There may currently be under-prescribing of treatments for men undergoing androgen ablation therapy. The new guidance may result in an increase of pharmacological treatments for this group. An MTA that assesses these drugs may result in a change in prescribing practice and patient choice. There may be a switch of people across the various drugs over time. If there is currently less than optimal use of drugs to treat the condition, the population may currently not be achieving the outcome benefits that potentially they could obtain. The publication of the guidance may cause this to be changed, and more people obtain the benefits of these drugs. This may see a reduction in other treatments for osteoporosis. A switch to orally administered drugs from those administered by IV infusion may be seen. The cost impact cannot currently be estimated.
Timeliness statement	Given that marketing authorisations have already been received for all but one of these technologies, issuing timely guidance will not be possible. As this will progress as a MTA, issuing timely guidance on the use of denosumab will also not be possible.

Provisional Title	Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture		
Topic Selection ID Number	4584	**Wave/Round**	R27
TA ID Number	621		
Manufacturer	Pfizer and Auxilium Pharmaceuticals. Pfizer and Auxilium Pharmaceuticals will conclude the collaboration agreement for CCH, effective April 24th, 2013. ***CONFIDENTIAL***		
Anticipated licensing information	Received marketing authorisation in Feb 2011. “Xiapex is indicated for the treatment of Dupuytren’s contracture in adult patients with a palpable cord.”		
Draft remit	To appraise the clinical and cost effectiveness of collagenase clostridium histolyticum within its licensed indication for the treatment of Dupuytren's contracture in adult patients with a palpable cord.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of collagenase clostridium histolyticum for the treatment of Dupuytren's contracture is appropriate. Population: Consultees suggested that the population should be defined using the mild, moderate and severe categories defined in the British Society for Surgery of the Hand (BSSH) guidelines. These guidelines recommend collagenase clostridium histolyticum (CCH) for treatment of Dupuytren’s contracture that is classified as moderate. However, consultees stated that CCH is also used to treat Dupuytren’s contracture classified as severe and mild, but stated that access for the mild Dupuytren’s contracture was limited as PCTs consider it too expensive. Comparators: Consultees agreed that surgery was the most appropriate comparator and that fasciectomy was currently the gold standard treatment for Dupuytren’s contracture. No changes to comparators. Outcomes: Attendees at the scoping workshop agreed that time to reduction of contracture should be replaced by time to return of normal function. MTA/STA: Consultees emphasised that a clinical guideline for Dupuytren’s disease would be most suitable due to the need for guidance on the treatment pathway (to establish when surgery is appropriate or when CCH is appropriate). However, it was discussed that as a clinical guideline is not currently planned, and given that the technology has been available since 2011 without any guidance available to the NHS, an MTA was appropriate.		
Process (MTA/STA)	MTA		

Population size	In England and Wales in 2010-11, 16,364 people were diagnosed with palmar fascial fibromatosis (Dupuytren). A total of 12,696 cases were admitted to hospital for digital and palmar fasciectomy, and 943 for the revision of digital and palmar fasciectomy. The manufacturer calculated an average of just under 13,000 admissions for Dupuytren's contracture per year between 2003 and 2008.
Proposed changes to remit (in bold)	None.
Costing implications of remit change	No changes to costing comments are necessary.
Timeliness statement	Given that Collagenase clostridium histolyticum received a license in February 2011, issuing timely guidance for this technology will not be possible.