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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Methocarbamol/paracetamol-containing medicinal products

Methocarbamol/paracetamol

Procedure number: EMEA/H/A-31/1484

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Information on the procedure

The German National Competent Authority (NCA) (BfArM) is of the view that recent publications cast doubt on the efficacy of medicinal products containing methocarbamol/paracetamol 380 mg/300 mg in the "*short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders*" (Cochrane Database of Systematic Reviews, 2016 [1]; Emrich, 2015 [2]; Luis-Miguel Gonzalez-Perez, 2015 [3]; Oliveras-Moreno, 2008 [4]). In addition, it is unclear whether any interaction may be expected when both substances are administered in combination (Bruce, 1971 [5]; Micromedex, 2014 [6]).

On 27 May 2019 the BfArM therefore triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of medicinal products containing methocarbamol/paracetamol 380 mg/300 mg. The CHMP should give its opinion whether the relevant marketing authorisations should be granted, maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Methocarbamol is a centrally acting muscle relaxant. It produces its muscle-relaxant effect by inhibiting polysynaptic reflexes in the spinal cord and subcortical centres. Paracetamol is an analgesic with antipyretic properties. It is thought to increase the pain threshold by inhibiting prostaglandin synthesis, by means of blocking cyclooxygenase enzymes (specifically COX-3) in the central nervous system and, to a lesser extent, in peripheral tissues. Its antipyretic effect is related to the inhibition of Prostaglandin E1 (PGE1), synthesis in the hypothalamus.

In the EU/EEA a fixed dose combination (FDC) medicinal products containing methocarbamol/paracetamol 380 mg/300 mg was first authorised in Spain in 1985 under the name Robaxisal, for use in the "*short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders*". In adults the posology is 2 tablets every 4-6 hours (four to six times daily), depending on the severity of the symptoms. Hence the maximum daily dose is methocarbamol/paracetamol 4560 mg / 3600 mg (12 tablets). Common musculoskeletal conditions causing tenderness and muscle spasms include fibromyalgia, tension headaches, myofascial pain syndrome, and mechanical low back or neck pain (Chou, 2004).

Of note, Robaxisal was first authorised in Spain in 1968 as FDC of methocarbamol and acetylsalicylic acid (ASA). ASA was replaced by paracetamol in 1985 in view of its more favourable safety profile. During the assessment of a generic marketing authorisation application (MAA) in the United Kingdom

[1] Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. Cochrane Database Syst Rev. 2016 Jun 7;(6):CD012230.
[2] Emrich 0M, Milachowski KA, Strohmeier M. [Methocarbamol in acute low back pain. A randomized double-blind controlled study]. MMW Fortschr Med. 2015 Jul;157 Suppl 5:9-16.
[3] Luis-Miguel Gonzalez-Perez (2015): Deep dry needling (DDN) of trigger points located in the lateral pterygoid muscle(LPM): Efficacy and safety of treatment for management of myofascial pain and temporomandibular dysfunction. Med Oral Patol Oral Cir Bucal. 2015 May 1;20 (3):e326-33.
[4] Oliveras-Moreno IM et al (2008): Efficacy and safety of sodium hyaluronate in the treatment of Wilkes Stage II Disease. J Oral Maxillofac Surg 66:2243-2246.
[5] Bruce RB, Turnbull LB, Newman JH. Metabolism of methocarbamol in the rat, dog, and human. J Pharm Sci. 1971;60(1):104-6.
[6] Drug Details Micromedex: Acetaminophen. 2014.

and Germany for this FDC, BfArM raised concerns on the efficacy and questioned the safety of these products.

Specifically, BfArM considered that the results of a Cochrane review of paracetamol for low back pain (LBP) and the results of a randomised controlled trial (RCT) of a medicinal product containing methocarbamol 750 mg as mono-component for low back pain cast doubt on the efficacy of methocarbamol/paracetamol 380 mg/300 mg (Cochrane Database of Systematic Reviews, 2016 [1]; Emrich, 2015 [2]). They further noted that no clinical trial investigated this FDC against the mono-component or placebo, and that the only two trials investigating the FDC in 380 mg/300 mg strength showed lower efficacy than deep dry needling or hyaluronate infiltrations in temporomandibular joint dysfunction (Luis-Miguel Gonzalez-Perez, 2015 [3]; Oliveras-Moreno, 2008 [4]). BfArM also considered that clarification was needed whether any interaction may be expected when both substances are administered in combination in view of the fact that they are both metabolised in the liver and conjugated to glucuronic and sulfuric acids (Bruce, 1971 [5]; Micromedex, 2014 [6]).

The BfArM therefore considered it in the interest of the Union to review the impact of the above concerns on the benefit-risk balance of medicinal products containing methocarbamol/paracetamol 380 mg/300 mg for use in the short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders at EU level.

In its assessment, the CHMP considered the totality of the data submitted. A summary of the most relevant data is included below.

According to the IMS data, from 2009 to 2018, the majority of prescriptions reported a therapeutic indication falling into the following disorders: other dorsopathies (57.32%), deforming dorsopathies (9.69%), injuries to the neck (5.94%), disorders of muscles (5.62%), other soft tissue disorders (3.52%) injuries to the thorax (3.19%), spondylopathies (2.22%) and diseases of oral cavity, salivary glands and jaws (2.06%) (those therapeutic indications with a percentage < 2 have not been listed). The disorder "no specific low back pain" belongs to the category of "other dorsophaties"; the percentage of prescriptions of Robaxisal for the treatment of low back pain ranged annually from 19.4% to 30.8%.

2.2. Data on efficacy

The MAH/applicant submitted data to support the efficacy of their medicinal products in the short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders. No RCT of the FDC against the mono-component or placebo are available. Most relevant data on the efficacy of each component alone and in combination with other active substances in painful muscle spasms is presented below.

2.2.1. Data on paracetamol mono-component

In line with the WHO´s recommendations, several studies have demonstrated the analgesic activity of paracetamol. Some of them have shown that paracetamol is equally effective to aspirin or phenacetin in producing analgesia in postpartum women (Lasagna, 1967), more effective than dextropropoxyphene in episiotomy pain relief (Hopkinson, 1973), and more effective than aspirin in pain relief after bilateral tooth extraction (Mehlisch, 1984). Moreover, Barden (2004) concluded in a meta-analysis that single-dose oral paracetamol is effective for the treatment of moderate to severe, acute postoperative pain, irrespective of the dose used (in the study paracetamol doses ranged from 325 to 1,500 mg). Several studies have also demonstrated the efficacy of paracetamol in musculoskeletal pain relief (William, 2005; Bondarsky, 2013; Yilmaz, 2018).

A recent review of the Cochrane Database raised concerns regarding the efficacy of paracetamol in low back pain and efficacy in this indication is further discussed below.

Saragiotto 2016 - Systematic review in the Cochrane Library of paracetamol for LBP

A systematic review in the Cochrane Library of paracetamol for LBP was conducted. The author's conclusions were the following: *"The results argue against the use of paracetamol in the management of acute low back pain. […] The high-quality evidence and precise estimate of no effect for acute LBP suggests that no additional trials of paracetamol for acute LBP are required. For acute LBP the research questions include establishing what analgesic medicine(s) should replace paracetamol as the first line analgesic for acute LBP; and evaluating if combination medicines containing paracetamol are effective"*

It should be noted that the indication "low back pain" is unspecific as the pain can be of muscular, neuronal or bone-related origin.

This systematic review included 3 RCTs in the qualitative synthesis and two of these were included in the meta-analysis (Wetzel, 2014 and Williams, 2014). The third trial was not included in the meta-analysis as no results were reported for the placebo arm (Nadler, 2002). Of note the Wetzel 2014 trial included only 40 participants, all with chronic LBP, and has recently been retracted. Most patients included in the review (90%) participated to the PACE trial (Williams, 2014). The authors of the Cochrane review rated the PACE trial at low risk of bias for all criteria. The PACE trial randomised middle-aged Australian patients with acute LBP to paracetamol (n=1096) or placebo (n=547). It should be noted that when calculating the sample size of the trial, a sample of *"1650 patients was defined to provide 80% power to detect a difference of 3 days in median time to recovery, with a two-sided α of 0.05 and allowing for 10% non-adherence"*. However, Williams reported a treatment non-adherence (participants consuming less than 70% of the recommended dose) of 51% for the paracetamol groups and a 47% for the placebo group. A post hoc analysis of the PACE study published one year after the Cochrane Review by Bier (2017) reported value of non-adherence to study medication increased to 57.5% (Bier, 2017). It is therefore questionable whether this study was adequately powered to detect a statistically significant difference between treatment arms.

Critical arguments raised on the publication of Williams 2014 as regards non-adherence to study medication have recently been re-analysed by Schreijenberg and colleagues (Schreijenberg, 2019 [7]). Using individual participant data from the PACE trial, complier average causal effect (CACE), intention-to-treat, and per protocol estimates were calculated for pain intensity (primary), disability, global rating of symptom change, and function (all secondary) after 2 weeks of follow-up. Compliance was defined as intake of an average of at least 4 of the prescribed 6 tablets of regular paracetamol per day (2660 mg in total) during the first 2 weeks after enrolment. Exploratory analyses using alternative time points and definitions of compliance were conducted. Mean between-group differences in pain intensity on a 0 to 10 scale using the primary time point and definition of compliance were not clinically relevant (propensity-weighted CACE 0.07 [-0.37 to 0.50] P = 0.76; joint modelling CACE 0.23 [-0.16 to 0.62] P = 0.24; intention-to-treat 0.11 [-0.20 to 0.42] P = 0.49; per protocol 0.29 [-0.07 to 0.65] P = 0.12); results for secondary outcomes and for exploratory analyses were similar. The authors concluded that paracetamol is ineffective for acute LBP even for patients who comply with treatment. However, the CHMP considered that such reanalysis cannot compensate for flaws in conduct of the initial study such as study power issue in the PACE trial. In addition, *post-hoc* analyses cannot not be considered as evidence of absence of efficacy, given their exploratory nature.

[7] Schreijenberg M, Christine Lin CW, McLachlan AJ, Williams CM, et al. Paracetamol is ineffective for acute low back pain even for patients who comply with treatment: complier average causal effect analysis of a randomized controlled trial. Pain 2019 Aug 23.

Therefore, considering the methodological standards identified in the PACE trial, in particular regarding treatment non-adherence, the CHMP considered that no conclusion can be drawn on the observed absence of difference between treatment groups.

Chou 2016

This review of non-invasive treatments for LBP found that for acute LBP, evidence suggested that NSAIDs (strength of evidence [SOE]: low to moderate), skeletal muscle relaxants (SOE: moderate), opioids (SOE: low), exercise (SOE: low), and superficial heat (SOE: moderate) are more effective than placebo, no intervention, or usual care, whilst paracetamol (SOE: low) and systemic corticosteroids (SOE: low) are no more effective than placebo. The authors conclusions regarding paracetamol are based on the above discussed PACE trial (Chou, 2016 [8]).

Miki 2018

This was a randomized open-label non-inferiority trial of paracetamol or loxoprofen in 127 Japanese patients with acute low back pain. As primary outcome measure, pain intensity was measured using a 0-10 numeric rating scale (NRS). The results suggest that paracetamol has comparable analgesic effects on acute LBP to loxoprofen, at 4 weeks. The authors concluded that paracetamol seems to be a reasonable first-line option for patients with acute LBP in Japan. Of note however, 50% of patients dropped out of the trial.

A number of older reviews of paracetamol in acute lower back pain are summarised in the table below.

Table 1. Older reviews of paracetamol in acute lower back pain

Reference	Condition	Number of patients	Method	Authors conclusions
Deyo 1996	LBP	-	Review of randomized trials and systematic literature syntheses	It seems reasonable to recommend paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with acute back pain.
Roelofs 2008	LBP	11,237	Systematic analysis of 65 RCT and controlled clinical trials. Acute low back pain (25 trials), chronic low back pain (9 trials) mixed or unclear low back pain population (31 trials) 6 trials NSAIDs versus paracetamol	For acute LBP, NSAIDs were no different for improvement in pain intensity vs. paracetamol (3 studies; SMD -0.21, 95% CI -0.43 to 0.02) One study found limited evidence that paracetamol was less effective than NSAIDs for chronic low back pain.
Reece 2008	LBP	676	Systematic review: 7 eligible trials were identified. 5 investigating acute LBP, 1 investigating chronic LBP and 1 investigating both (only small trials: patients <25). No trial compared paracetamol to placebo. Outcome data of post	No trial reported a statistically significant difference in favour of paracetamol. There is insufficient evidence to assess the efficacy of paracetamol in patients with low back pain. There is a clear need for large,

[8] Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, Fu R, Dana T, Kraegel P, Griffin J, Grusing S, Brodt E. Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Review No. 169. February 2016.

Reference	Condition	Number of patients	Method	Authors conclusions
			treatment pain and disability scores were extracted (such as visual analogue scales (VAS) numerical rating scales (NRS) or the Roland Morris disability questionnaire, were converted to a common 0–10 scale)	high quality randomized controlled trials evaluating paracetamol in patients with low back pain.
Duffy 2010	LBP	-	Review of literature and therapy recommendations for the treatment of low back pain	There are conflicting data as to whether paracetamol is equivalent, or slightly inferior, to NSAIDs for the treatment of low back pain. Paracetamol and NSAIDs are effective first-line medications for acute or chronic low back pain.
Machado 2015	spinal pain (neck or low back pain) and osteoarthritis	1825 patients with LBP	Systematic review and meta-analysis. This review included the 3 same trial as the 2016 Cochrane review described above. No other trials in LBP were included.	Paracetamol is ineffective in the treatment of low back pain. These results support the reconsideration of recommendations to use paracetamol in this condition

2.2.2. Data on methocarbamol mono-component

Methocarbamol was shown to provide an improvement in patients suffering from painful muscle processes (Beebe, 2005). In 1980, György studied the rational use of muscle relaxants in rehabilitation medicine, highlighting the usefulness of methocarbamol for acute trauma, muscle spasms, myalgia and different pain conditions, indicating the appropriateness in some cases of administration of analgesics. Furthermore, many researchers have shown the efficacy of methocarbamol in orthopedic conditions/alterations (Forsyth, 1958; Carpenter, 1958; Leventen, 1960; Lamphier, 1961), in muscle spasms (Valtonen, 1975; Tisdale, 1975) in severe flexor spasm associated to spinal diseases (O´Doherty, 1958), in muscle cramps (Perchuk, 1961; Abd-Elsalam, 2019), in craniomandibular disorders (Stanko, 1990), in postoperative breast surgery submuscular implants (Schneider, 1997), in low back pain (Sudarsini, 2014; Emrich, 2015; Überall, 2017), and in the reduction of hospital length of stay in patients with closed rib fracture injuries (Patanwala, 2017).

2.2.3. Data on fixed dose combination products containing methocarbamol and/or paracetamol

2.2.3.1. Studies with FDC of methocarbamol/paracetamol

Oliveras-Moreno 2008

This was an open, randomized, single centre, pilot study investigating in 41 patients with Wilkes stage II disease, the efficacy of a single intraarticular infiltration of sodium hyaluronate (SH) in significantly reducing pain and improving function in the temporomandibular joint, compared with the

administration of 2 tablets of Robaxisal, every 6 hours for 4 weeks. The main efficacy parameters for this trial were pain at rest, on jaw opening, and on mastication, measured on a 10-cm VAS. A statistically significant difference was observed for pain at rest in favour of the SH group (n=20). No improvement was observed for the efficacy parameters measures in the Robaxisal group (n=15).

Looke 2013

This was a retrospective cohort study of 300 patients, with 150 patients using a new perioperative pain protocol for primary total hip and knee replacement that included intravenous methocarbamol and intravenous paracetamol instead of preoperative oral analgesics (150 patients). The 2 cohorts were similar in patients' gender, age, and body mass index. Subgroup analysis suggested that changes to the hip protocol were responsible for decreased opioid use. The authors concluded that the significantly improvement in patient care observed was at least partially due to the change from previous protocol to the use of preoperative intravenous methocarbamol and intravenous paracetamol. The publication however neither outlines the previous perioperative pain protocol nor the concrete doses of the changed medication including methocarbamol and paracetamol. Of note, the new medication protocol resulted in reduced opiate use, however also in significantly increased pain (all periods) as measured on the VAS (5.5±1.2 vs 4.9±1.0). Further, the relevance of intravenous use of this substance combination in a perioperative setting to the intended use for methocarbamol/paracetamol 380 mg/300 mg tablet is questionable.

Saravanabhavan 2014

This was a prospective, randomized, single blind, single centre, comparative study. 201 patients with low back pain were randomized to receive either methocarbamol 500 mg p.o. thrice daily (group M) or thiocolchicoside 8 mg p.o. twice daily (group T), with paracetamol 650 mg p.o. twice daily for 7 days. The pain intensity, as measured by VAS, showed significant reduction of pain in both groups on day 3, and 7 but improvement was better in group M as compared to group T ($p<0.0001$). Hand-to-floor distance (HFD) and muscle spasm decreased significantly ($p<0.005$ for HFD, $p<0.006$ for visible and $p<0.0001$ for palpable spasm) on day 7 in group M as compared to group T. Mean % Oswestry disability index scores improved significantly on both day 3 and 7 ($p<0.0001$) in group M as compared to group T. Patients' global evaluation showed 80% of patients in group M evaluated the treatment as very good. Both treatments were well tolerated. The authors concluded that whilst methocarbamol is superior both treatments in combination with paracetamol are effective in acute LBP with spasm.

A number of limitation are however noted including major inconsistencies as regards pain measurements: it remains unclear whether paracetamol was administered twice daily or trice daily; no conclusions can be drawn on the spontaneous remission of (acute) LBP throughout the study population as no placebo group is included; the inclusion criterion is given as existence of LPB equal to or greater than 5mm on VAS, as a 0-10 cm VAS scale as outcome measure, but the results are given in the range of 302 – 736 without any unit; the statistical approach is described insufficiently, it is unclear how data obtained from whether the 27 "excluded" patients have been handled. Of note also the investigated single doses and the daily doses (1500mg / 1300 or 1950mg) are different from that of Robaxisal.

González-Pérez 2015

This was an open, randomized, single centre clinical trial investigating whether deep dry needling (DDN) of trigger points (TPs) in the lateral pterygoid muscle would significantly reduce pain and improve function, compared with methocarbamol/paracetamol medication. This combination was given to 24 patients as methocarbamol (380 mg) and paracetamol (300 mg), at a dose of two tablets every six hours for three weeks. Assessments were carried out pre-treatment, 2 and 8 weeks after finishing the treatment. A statistically significant difference ($p<0.05$) was detected for both groups with respect

to pain reduction at rest and with mastication. The improvement in the temporo-mandibular joint functionality was statistically significant on days 28 and 70 of the study for both groups. No placebo group was included, thus, no conclusions can be drawn on the spontaneous remission of myofascial pain throughout the study population within the observational period.

Yeom 2017

This observational study investigated the efficacy of methocarbamol in combination with paracetamol for the treatment of muscle pain in comparison to other treatments including NSAIDs. The 90 patients enrolled with musculoskeletal disease (muscle pain including back pain) were separated based on level of pain and severity into 3 groups of 30 patients each: Group 1, group 2 and group 3 corresponding to mild, moderate and severe pain respectively. To measure the pain, the Alice Rich´s "0~10 Comparative Pain Scale" was used. Group 1 received (paracetamol 650 mg tablets + ibuprofen 200 mg tablets) 3 times a day for 7 days, group 2 received (paracetamol 650 mg tablets + naproxen or ibuprofen 200 mg) 3 times a day for 7 days in addition to methocarbamol 500 mg tablets 3 times a day during the first 2 day, while Group 3 received paracetamol 650 mg tablet 3 times a day for 7 days + methocarbamol 500 mg 3 times a day for the first 2 days. Group 3 was also instructed to stretch 3 times a day for the duration of the treatment. After evaluation of the results, it was concluded that the drug combination of the methocarbamol 500 mg, paracetamol 650 mg and ibuprofen 200 mg tablets yielded similar benefits as the methocarbamol 500 mg and paracetamol 650 mg tablets paired with physical stretching exercises regarding overall pain control.

No placebo group was included, thus, no conclusions can be drawn on the spontaneous remission of muscle pain throughout the study population. Pain measurements were only performed after 2 weeks, while treatment was stopped after 1 week. It is questionable, whether with this time interval a real treatment effect can be captured in the selected patient population with (acute) muscle pain. Further pain was measured on the Alice Rich's Comparative pain scale and not on the recommended well-established VAS or NRS pain scales. The investigated single doses were 500mg Methocarbamol/ 650mg Paracetamol, the daily doses 1500mg / 1950mg, which differ from the product under discussion.

2.2.3.2. Studies with FDC containing methocarbamol or paracetamol in painful muscle spasms

Results of a number of RCT evaluating the efficacy of fixed-dose combination products including either paracetamol or methocarbamol, in painful muscle spasms, have been published and are summarised in the below table.

Table 2. RCT with fixed-dose combination products including either paracetamol or methocarbamol, in painful muscle spasms

Reference	Patients	Study design	Methocarbamol and paracetamol dose and regimen	Results and comments
Bondarsky 2013	90 pts emergency department patients with musculoskeletal pain scores greater than 0	R, DB	Paracetamol: 1g	Pain decreased over the one-hour study period for all groups (P < .001) with mean (SD) scores about 20 mm lower on the VAS than the mean initial score. However, there was no significant difference among treatment groups (paracetamol alone, ibuprofen alone or

Reference	Patients	Study design	Methocarbamol and paracetamol dose and regimen	Results and comments
				paracetamol plus ibuprofen) (P = .59). The need for rescue analgesics was similar across groups. The study had 33% powered to detect differences among the groups in need for rescue medication.
Gready 1976	49 pts (16 – 77 y) with cervical and lumbar sprains, bursitis, myositis, and tendonitis	R, DB	Methocarbamol: 2 x 400mg q.i.d. for 8 days Paracetamol: 2 x 300mg q.i.d. for 8 days	Chlorzoxazone 250 mg plus paracetamol 300 mg was significantly superior to methocarbamol 400 mg plus aspirin 325 mg (similar until day 2) in relieving the symptoms of skeletal muscle spasm. Physical therapy was allowed during the study, but additional analgesics and muscle relaxants were not given.
Middleton 1984	107 pts (17 – 77 y) with low back pain from lumbar muscle spasm	R, SB	Methocarbamol: 2 x 400mg t.i.d. for 7 days Paracetamol: 2 x 450mg t.i.d. for 7 days	Similar efficacy between methocarbamol 400 mg plus aspirin 325 mg and chlormezanone 100 mg plus paracetamol 450 mg. Analgesics, muscle relaxants, sedatives, tranquilizers, and physiotherapy during the study were not allowed.
Vernon 1972	183 pts (18 – 64 y) with various musculoskeletal syndromes (mostly acute lumbo-sacral strain)	R, DB, PC	Paracetamol: 2 x 300mg q.i.d. for an average of 6 days	Chlorzoxazone 250 mg plus paracetamol 300 mg was superior to chlorzoxazone alone and to placebo.
Walker 1973	59 pts (17 – 60 y) with acute musculoskeletal disorders, but always including lumbosacral pain and spasm in each case	R, DB, PC	Paracetamol 2 x 300mg q.i.d. for 10 days	Chlorzoxazone 250 mg plus paracetamol 300 mg was significantly better compared to chlorzoxazone alone (on days 2 and 4) or to placebo
Daunas 1973, Tisdale 1978	302 pts (mean 40 y) with acute and painful localised skeletal muscle tensions after trauma and/or inflammation	R,DB, PC	Methocarbamol: 3 x 400 mg q.i.d. (up to 48h), then 2 x 400 mg q.i.d. for further 6 days	400 mg methocarbamol plus 325 mg aspirin was superior to methocarbamol (400 mg), aspirin (325 mg), and to placebo. Statistical significance was reached over aspirine and placebo at 48h and over placebo at day 8.

R; randomised; DB: double blind; SB: single blind, PC: placebo control

2.2.4. Discussion

Data from high quality controlled clinical trials on combination treatments of acute musculoskeletal disorders is limited (Bannwarth 2013, Chou 2016). This may in part be related to the fact that many therapeutic entities (like paracetamol and methocarbamol) are based on medical experience, rather than on clinical trials with 'state-of-the-art' methodological standards that have significantly developed over the past 30 years. Further, Robaxisal was initially authorised as a fixed dose combination of methocarbamol and acetylsalicylic acid. No clinical trial testing the superiority in efficacy of a methocarbamol/paracetamol combination over the single compounds alone was identified. However, there is data on combination therapies in the treatment of painful muscle spasms in acute musculoskeletal disorders, particularly for low back pain, as discussed below.

Under the assumption that methocarbamol 400 mg was similarly effective compared to chlorzoxazone 250 mg, the data published by Gready (1976) suggest that paracetamol 300mg (in the combination with chlorzoxazone) is at least as effective as aspirin 325 mg (in the combination with methocarbamol) during the first 2 days after start of treatment. Under the same assumption, the data published by Middleton (1984) would suggest that paracetamol 450 mg is similarly effective to aspirin 325 mg when given in combination to a muscle relaxant. Although these qualitative cross-comparisons may not be stressed too far, they may provide some information on the performance of the single compounds when given in combination to other drugs. Further, the data published by Bondarsky (2013) suggest that paracetamol was as effective as ibuprofen.

Data published by Vernon (1972) and Walker (1973) show that the muscle relaxant chlorzoxazone 250 mg in combination with paracetamol 300 mg is superior to chlorzoxazone 250 mg alone, suggesting that paracetamol significantly adds to the effect of the muscle relaxant alone. Similarly, data published by Daunas (1973) and Tisdale (1978) showed that methocarbamol 400 mg in combination with aspirin 325 mg is superior in short-term efficacy when compared to the single components, suggesting that methocarbamol significantly adds to the effect of the analgesic alone. Dose strengths of paracetamol (300, 450 mg) and of methocarbamol (400 mg) in these studies were identical (paracetamol) or similar (methocarbamol) to the dose strength in the FDC subject of this review and daily doses were equal or below that foreseen in the posology of this FDC. In these studies, FDC products including either paracetamol or methocarbamol were shown to be effective in the acute treatment of painful muscle spasms (Gready 1976, Middleton 1984, Bondarsky 2013). Studies of fixed dose combinations with paracetamol have shown the additive effect of paracetamol 300mg when given in a fixed dose combination with a muscle relaxant (Vernon 1972, Walker 1973). Studies of fixed dose combinations with methocarbamol have proven the additive effect of methocarbamol 400mg when given in a fixed dose combination with an analgesic (Daunas 1973, Tisdale 1978). Both FDC products had significantly different effects from placebo (Vernon 1972, Walker 1973, Daunas 1973, Tisdale 1978).

Whilst these studies provide a rational for the efficacy of the FDC of methocarbamol/paracetamol 380 mg/300 mg, it should be noted that these are mostly small studies presenting a number of methodological issues (e.g. flaws in the design, adherence/sample size, concomitant treatments which may impact on the results). Further these studies do not provide information as to whether the product may be used as "first-line", "add-on", or "switch" as is currently required in the guideline on FDC (EMA/CHMP/158268/2017).

The studies with fixed dose combinations of methocarbamol/paracetamol do not bring new relevant information on the efficacy of the FDC containing methocarbamol/paracetamol 380 mg/300 mg tablet. The Oliveras-Moreno (2008) study was a small open study comparing robaxisal to intraarticular infiltration of sodium hyaluronate. In the Looke (2013) study, intravenous methocarbamol and

paracetamol were compared to oral analgesics in perioperative pain for primary total hip and knee replacement, the relevance of which is questioned for the intended use of the fixed dose combination. A number of methodological limitations were identified in the Saravanabhavan (2014) study, which investigated lower daily doses of both substance than expected with the FDC containing methocarbamol/paracetamol 380 mg/300 mg. The Gonzales-Perez study (2015) was a small open label study in which no placebo group was included. In the Yeom (2017) study, no placebo arm was included either, the single and daily doses investigated differed from those expected to be used with the FDC containing methocarbamol/paracetamol 380 mg/300 mg and a few methodological limitations were noted such as the time interval between end of treatment and pain measurement and the pain scale used.

Efficacy of paracetamol in low back pain

With regards to the efficacy of the paracetamol component in lower back pain, whilst older studies were supportive of such effectiveness, Williams further to its 2014 study (PACE) and later reviews mainly based on that study (Machado, 2015; Choux, 2016; Saragiotto Cochrane review, 2016) and a re-analysis of the same study (Schreijenberg, 2019) pointed to the lack of efficacy of paracetamol in that indication. The substantial lack of adherence to study medication, has however been identified as an important limitation questioning the ability of the PACE study to detect a true difference between treatment arms. The re-analysis conducted by Schreijenberg in 2019 cannot, by nature, provide reassurance on flaws in the conduct of the study, as *post-hoc* exploratory analyses cannot alleviate the deficiencies found in the main analysis. Mikki conducted an open-label, non-inferiority study in 2018, supportive of an effect of paracetamol in lower back pain. It should be noted however that half of the patients dropped out of the study, hence also questioning the capacity of the study to detect a difference between treatment arms. Recommendations from treatment guidelines were also noted, including the fact that the use of paracetamol is no longer recommended in some of these, again based on the Cochrane Review of Saragiotti (2016) discussed above. Overall, the CHMP considered that there were no significant new elements that would question the efficacy of paracetamol in lower back pain.

Adequacy of the dose

One of the issues raised in the notification was linked to the recently authorised medical product containing methocarbamol 750 mg mono-component in the symptomatic treatment of painful muscle tension in adults, in particular low back pain (lumbago). The efficacy of this product was demonstrated when administered at the following doses: "1500 mg three times a day. At the beginning of treatment, a dose of 1500 mg four times a day (6000 mg) is recommended. In severe cases up to 7500 mg methocarbamol per day can be taken."

The authorised posology of methocarbamol/paracetamol 380 mg/300 mg is methocarbamol/paracetamol 3040 to 4560 mg / 2400 to 3600 mg. Hence the maximum daily dose of methocarbamol in the FDC is similar to the recommended daily dose for methocarbamol 750 mg past the beginning of treatment, however the single dose of methocarbamol 750 mg is twice as high.

Nevertheless, as discussed above, in the studies investigating FDC products including either paracetamol or methocarbamol, the administered doses of paracetamol and of methocarbamol were similar to the dose strength of the single components as contained in the FDC methocarbamol/paracetamol 380 mg/300 mg. Daily doses were also either similar or lower in these studies.

In conclusion, there are no new elements indicating that the doses in the FDC with methocarbamol/paracetamol 380 mg/300 mg might be too low.

Conclusion on efficacy

In conclusion, the CHMP is of the view that the data available does not constitute sufficient evidence to question the efficacy of methocarbamol/paracetamol 380 mg/300 mg tablet in the short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders.

It is noted however that no RCT of the FDC against the mono-component or placebo are available, thus the MAH/applicant are recommended to perform such study.

2.3. Data on safety

The MAH/applicant presented a review of all safety information with regards to the FDC methocarbamol/paracetamol 380 mg/300 mg, with a particular focus on a possible pharmacokinetic interaction between both substances when are administered concomitantly.

2.3.1. Non-clinical

The MAH/applicant specifically discussed the risk of possible interactions leading to an increase of the toxic metabolite of paracetamol N-Acetyl-p-benzoquineimine taking into account that both substances are metabolized in the liver and conjugated to glucuronic and sulfuric acid.

As mentioned previously, 4560 mg methocarbamol and 3600 mg of paracetamol are the maximal amount of active ingredients to be administered within 24 hours. The total amount of paracetamol absorbed is metabolised at 40 % by sulfation. The sulfation of methocarbamol amounts to much less than 40-50%, as the total amount of the absorbed substance undergoes phase II metabolism reactions by both glucuronidation and sulfation. In this context, it is relevant to underline that toxicity to paracetamol develops at 7.5 to 10 g/day or 140 mg/kg of active substance per day (Agrawal 2018). Therefore, approximately twice as much as the maximal daily dose for the FDC. Taking into consideration the metabolism rates of the active substances, probability for an increase of the toxicological relevant NAPQI or another risk for a safety concern due to the combination of active substances is considered low.

This is further supported by data of the admetSAR server, which elaborates predictions based on the literature and the structure-activity relationship of drug candidates. According to this database, there is a high probability that methocarbamol is not substrate or inhibitor of hepatic cytochromes like CYP450 2C9, 2D6 and 3A4 (although this last enzyme has a lower probability to be a metaboliser of methocarbamol, as per in-silico data) (DrugBank 2019), which would rule out the possibility of an interaction between the metabolic pathways of the two active substances. Authors of a recent study comparing the efficacy of different combination of pain medication and stretches also considered, based on previous research, that there is no overlap between the enzyme that metabolise paracetamol and methocarbamol (Yeom et al. 2017).

No interaction between paracetamol and methocarbamol has been demonstrated to date. As both active substances have different therapeutic and adverse effects, a pharmacodynamics interaction between the active substances is unlikely.

2.3.2. Clinical

2.3.2.1. Hepatotoxicity

Overall 9 ISCRs reporting hepatotoxicity with methocarbamol/paracetamol as suspected drug were identified. Out of these 3 reported a suspected drug the triple combination ibuprofen/methocarbamol/paracetamol and are not further discussed. In addition, for 3 of these cases,

the causality relationship using the WHO-UMC scoring was classified as unlikely (1) or unassessable (2). For the remaining 3 cases the causality was assessed as possible.

In the 3 cases possibly related to the fixed dose combination methocarbamol/paracetamol, the reported events were overdose for 3 months and related events of hepatitis and hyperbilirubinemia, hepatic pain and hepatic function decreased/elevated liver enzymes/liver disorder in a patient suffering from gastroenterohepatic neuroendocrine tumour.

These do not bring new information with regards to the risk of hepatotoxicity with methocarbamol/paracetamol containing products and the product information is considered up to date in this regard.

2.3.2.2. Other adverse events

A search in the database of the originator retrieved a total of 22 ICRS associated with the use of Robaxisal. Out of these the following 14 AEs from 12 ICSRs were considered unexpected: acute pulmonary oedema, diarrhoea, mouth ulceration, dry mouth, oral discomfort, melaena, anhedonia, depression, hypoesthesia, extrapyramidal disorder, pallor, hypersensitivity vasculitis, gait disturbance and oedema peripheral. Causality assessment was performed for each unexpected AE and a cumulative review performed for those classified as probably related to the FDC.

Diarrhoea: Two ICSRs reporting diarrhoea after Robaxisal use have been retrieved from the MAH's safety database. One of these was serious and occurred during the first day of treatment and was assessed as probably related to while the other one occurred during the third day of treatment. In both cases, the events resolved after treatment cessation. Applying the WHO-UMC scoring system, the serious case was assessed as probably related to Robaxisal and the non-serious case as possibly related. A further 3 cases were identified in EudraVigilance, all of them reporting an early onset of the events after start of treatment but all cofounded by other medicinal products. The CHMP considered that in the present cases diarrhoea did not appear to be an early symptom of paracetamol-induced hepatotoxicity and that its inclusion in the product information was warranted.

Dry mouth/oral discomfort: In total one serious case of dry mouth, oral discomfort and dyspepsia was reported. This case was not medically confirmed. The events developed after a 25-day treatment with Robaxisal for lower back pain. The patient recovered following treatment interruption. Using WHO-UMC scoring system, the causal relationship between Robaxisal and the reported AEs has been assessed as probable. Scientific data have shown that methocarbamol has anticholinergic properties and therefore may induce dry mouth. The CHMP considered that the product information should be updated accordingly.

For the other cases, either insufficient information was in fact available to perform a causality assessment (mouth ulceration), or confounders and/or more plausible explanations were reported and/or no data supportive of such reaction was identified in the literature (acute pulmonary oedema, anhedonia/depression, extrapyramidal disorder, hypoesthesia, hypersensitivity vasculitis and melaena), or they were symptoms of hypersensitivity reactions which is already listed (pallor, gait disturbance and oedema peripheral). The CHMP considered that no changes to the product information was needed in this regard.

2.3.3. Discussion

Whilst the risks regarding the potential pharmacokinetic interaction between paracetamol and methocarbamol have not been studied, this interaction has been observed neither for methocarbamol nor for paracetamol and the data from post-marketing sources do not suggest a higher risk of

hepatotoxicity (which could be the clinical result of this interaction) with the use of both active substances in combination. Indeed, overall 9 ISCRs reporting hepatotoxicity with methocarbamol/paracetamol as suspected drug were identified and those do not bring new relevant information to what is already described in the product information.

Pharmacokinetic interaction studies with respect to the combination of both active substances are furthermore in accordance with "Guideline on the investigation of drug interactions" only required in case in case that "*there are indications that the interaction profile may not be adequately predicted from in vitro and in vivo interaction data for the separate drugs*". As sufficient data on the possible interactions for the mono-component has been published, there is no need for additional pharmacokinetic data of the combination.

In conclusion, conduct of pharmacodynamics interaction studies are not considered necessary.

Both active substances are well known, and their safety profile has been extensively described in several studies and publications. The CHMP concluded that no new significant information was identified with regards to the overall safety profile of the fixed dose combination methocarbamol/paracetamol. However, the adverse reactions 'dry mouth' and 'diarrhoea' were considered as at least possibly related to the methocarbamol component and as such are added to the product information with a frequency unknown. Information from the other cases did not warrant changes to the product information as either the information did not allow to establish a causal link, or they represented symptoms of adverse reactions already included in the product information.

The presentation of the tabulated lists of adverse reactions in section 4.8 of the SmPC was reformatted in line with the SmPC guideline (i.e. all adverse reactions should be presented in a single table, indicating which particular adverse reaction is usually attributable to which active substance in footnotes). It was noted that a few ADRs were not reflected under the correct SOC or with the appropriate PT and this was corrected for 'fatigue', 'somnolence', 'muscle incoordination', 'dysgeusia (metallic taste)', 'angioedema', sever skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis)', sterile pyuria (cloudy urine), 'adverse renal disorders'. In section 4 of the package leaflets adverse reactions were reorganised under their frequencies following the QRD template and in line with information in the SmPC, further, more patient friendly terminology was used where possible.

3. Benefit-risk balance

Methocarbamol is a centrally acting muscle relaxant. It produces its muscle-relaxant effect by inhibiting polysynaptic reflexes in the spinal cord and subcortical centres. Paracetamol is an analgesic with antipyretic properties. It is thought to increase the pain threshold by inhibiting prostaglandin synthesis, by means of blocking cyclooxygenase enzymes (specifically COX-3) in the central nervous system and, to a lesser extent, in peripheral tissues. Its antipyretic action is related to the inhibition of Prostaglandin E1 (PGE1), synthesis in the hypothalamus.

In the EU/EEA a fixed dose combination (FDC) medicinal products containing methocarbamol/paracetamol 380 mg/300 mg was first authorised in Spain in 1985 under the name Robaxisal, for use in the "short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders". In adults the posology is 2 tablets every 4-6 hours (four to six times daily), depending on the severity of the symptoms. Hence the maximum daily dose is methocarbamol/paracetamol 4560 mg / 3600 mg (12 tablets).

The CHMP considered all available data on the efficacy and safety of methocarbamol/paracetamol from clinical trials, the literature and from post-marketing reports.

No clinical trial testing the superiority in efficacy of a methocarbamol/paracetamol combination over the single compounds alone was identified. However, there is data on these active substances in the treatment of painful muscle spasms in acute musculoskeletal disorders, particularly for low back pain. Indeed, the literature provides some evidence of efficacy of the mono-components and some evidence of their additive effect when given in FDC with respectively a muscle relaxant or an analgesic. Of note, these studies do not provide information as to whether the product may be used as "first-line", "add-on", or "switch" as is currently required in the guideline for FDC.

The more recent studies of fixed dose combinations of methocarbamol/paracetamol do not bring new relevant information on the efficacy of the FDC containing methocarbamol/paracetamol 380 mg/300 mg as their designs were inadequate.

Older studies were supportive of the efficacy of the paracetamol component in lower back pain, while conflicting results were obtained in more recent studies. A number of limitations were identified in those recent studies and CHMP concluded that these, or the reviews relying on these results, did not bring significant new elements raising serious doubt on the efficacy of paracetamol in lower back pain.

Considering the posology of other methocarbamol-containing medicinal products and the doses used in clinical trials, the CHMP concluded that there is no indication that the doses in the FDC with methocarbamol/paracetamol 380 mg/300 mg might be too low.

In conclusion, whilst limitations were identified to the data available in support of the efficacy of methocarbamol/paracetamol 380 mg/300 mg in the short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders, no data constituting sufficient evidence to question the efficacy was identified.

No pharmacokinetic interaction was observed for paracetamol and/or methocarbamol and the data from post-marketing sources do not suggest a higher risk of hepatotoxicity with the use of both active substances in combination. Therefore, and as sufficient data on the possible interactions for the mono-component is available, there is no need for additional pharmacovigilance or pharmacodynamic studies of the combination.

The CHMP concluded that no new significant information was identified with regards to the overall safety profile of the fixed dose combination methocarbamol/paracetamol. However, the adverse reactions 'dry mouth' and 'diarrhoea' were considered as at least possibly related to the methocarbamol component and as such are added to the product information with a frequency unknown. Furthermore, section 4.8 of the SmPC and section 4 of the package leaflet are being reformatted in line with the SmPC guideline and QRD template.

In conclusion, the CHMP considers the above issues do not impact the benefit-risk balance. Therefore, the benefit-risk balance of methocarbamol/paracetamol 380 mg/300 mg containing products for use in short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders remains favourable subject to changes to the product information as described above.

4. Risk management

4.1. Amendments to the product information

The CHMP considered that amendments to section 4.8 of the SmPC were necessary.

'Dry mouth' and 'diarrhoea' are added as adverse reactions with the frequency 'not known'.

The tabulated listing of adverse reactions in 4.8 was reformatted in line with the SmPC guideline.

The Package Leaflet was amended accordingly.

5. Grounds for Opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for methocarbamol/paracetamol 380 mg/300 mg containing products.
- The CHMP considered the totality of the data available for methocarbamol/paracetamol 380 mg/300 mg containing products for use in short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders.
- The CHMP considered that, despite limitations, available data provided evidence of efficacy in the authorised indication and that no evidence raising serious doubts on the efficacy was identified.
- The CHMP further considered that the safety profile of both mono-components is well characterised, and no new significant evidence was identified for the fixed dose combination.

In view of the above, the Committee considers that:

a. the benefit-risk balance of methocarbamol/paracetamol 380 mg/300 mg containing products remains favourable subject to the agreed amendments to the product information. The Committee, consequently, recommends the variation to the terms of the marketing authorisations for methocarbamol/paracetamol 380 mg/300 mg containing products.

b. the issues raised in the notification triggering the present procedure dated 27 May 2019 do not impact the benefit-risk balance, and hence, do not preclude the granting of a marketing authorisation for the methocarbamol/paracetamol 380 mg/300 mg application, subject to the agreed amendments to the product information.