NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Germany:

Product Name(s) in the Referring Member State	Products containing Methocarbamol / Paracetamol See Annex I
Active substance(s)	Methocarbamol / Paracetamol
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	Oral use
Applicant / Marketing Authorisation Holder in the referring Member State	Various. See Annex I.

Background

[redacted] The originator product is Robaxisal compuesto (380/300 mg, tablet) by FAES FARMA, S.A., registered nationally only in Spain since 12 December 1968. It is used for the short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders. The procedure was started on 29 January 2019.

The dose recommendations for Robaxisal compuesto, 380/300 mg tablets are:

Single dose	Maximum dose

Two tablets (corresponding to **760mg** Methocarbamol / **600mg** Paracetamol) every 4-6 hours, depending on the severity of the symptoms.	The maximum dose of 12 tablets in 24 hours should not be exceeded (corresponding to a daily maximum dose of **4560mg** Methocarbamol / **3600 mg** Paracetamol).

The most recent publications strongly suggest that a B/R review is warranted for Robaxisal compuesto (380/300 mg, tablet) based on lack of efficacy in the proposed indication.

Issues to be considered

The BfArM was informed by the Spanish medicines agency (AEMPS) that Robaxisal compuesto (380/300 mg, tablet) was nationally authorised in 1968 according to the state of the art and the AEMPS confirmed that the Marketing Authorisation complied with the Acquis communautaire.

Paracetamol as single agent has been reported (Cochrane Database of Systematic Reviews 2016[1]) to be reliably ineffective in the treatment of low back pain, which is the one of the most common diagnosis included in Robaxisal's indication "painful muscle spasms associated with acute musculoskeletal disorders". Although generally both active substances have a good tolerability on their own, it is not acceptable to pose patients at any risk of an adverse event, in case there are uncertainties about efficacy. This accounts in particular in non-life-threatening diseases as included in the indication.

Methocarbamol as single agent (oral formulation) is approved in Germany for symptomatic treatment of painful muscle tension, especially in the lower back (lumbago). The originator product in Germany is Ortoton, 750 mg film-coated tablets by Recordati Pharma GmbH, registered since 02 September 2005, Reg. No. 6739691.00.00. The original approval for Ortoton, 750 mg film-coated tablets is mainly based on a randomized double-blind controlled study in acute low back pain. This study was conducted in 2002 and published in 2015[2].

Notable, the tested and efficacious single dose of Ortoton, 750 mg film-coated tablets is twice as high as for Robaxisal compuesto (380[3]/300 mg, tablet):

Single dose	Maximum dose
At the beginning of treatment **1500mg** methocarbamol 4 times a day, later recommended 1500mg methocarbamol 3 times a day.	In severe cases up to **7500mg** methocarbamol per day can be taken.

Scientific interest in the combination of methocarbamol and paracetamol seems to be very low throughout the last 50 years. Only four publications were found investigating the combination of methocarbamol and paracetamol. None of the trials were placebo-controlled or investigated the combination product in comparison to the single substances. Only two small open label trials included the proposed dosage for Robaxisal, revealing inferior efficacy in comparison to DDN[3] or hyaluronate infiltrations in temporomandibular joint dysfunction[4].

In light of the above mentioned scientific evidence that has become available since original approval, DE considers that the use of Robaxisal compuesto, 380/300 mg tablets in the claimed indications is not supported.

Furthermore, both active substances are metabolized in the liver and conjugated to glucuronic and sulfuric acid[5,6]. It is currently unclear, whether any interactions, especially an increase of the toxic metabolite N-Acetyl-p-benzoquinoneimine (of paracetamol) may be expected when administered in combination.

In view of the above and the necessity to take an action at EU level, Germany considers that it is in the interest of the Union to refer the matter to the CHMP in order to assess in particular the above mentioned evidence on the efficacy, and any possible interactions as regards to their impact on the benefit-risk balance of 380 mg methocarbamol / 300 mg paracetamol containing medicinal products, including pending applications, for use in the short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders.

The CHMP is requested in particular to give its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of medicinal products containing methocarbamol / paracetamol should be granted, maintained, varied, suspended or revoked.

References

1. Saragiotto BT1, 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 OM1, 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 JM et al (2008): Efficacy and safety of sodium hyaluronate in the treatment of Wilkes Stage II Disease. J Oral Maxillofac Surg 66:2243-2246Bruce RB, Turnbull LB, Newman JH.
5. Metabolism of methocarbamol in the rat, dog, and human. J Pharm Sci. 1971;60(1):104-6.
6. Drug Details Micromedex: Acetaminophen. 2014.

Signed [redacted]

Date 27. Mai 2019