EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Paracetamol/ibuprofen 500 mg / 150 mg Film coated tablets and associated names

INN/active substance: paracetamol/ibuprofen 500 mg / 150 mg

Procedure number: EMEA/H/A-29(4)/1447

Note:

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

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List of abbreviations

AEs	Adverse Events
CHMP	The Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CMS	Concerned member states
FDC	Fixed Dose Combination
IBU	Ibuprofen
LoOI	List of Outstanding Issues
LoQ	List of Questions
MAA	Marketing Authorisation Applicant
NNT	Number Needed to Treat
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PAR	Paracetamol
PIL	Product Information Leaflet
PSRPH	Potential Serious Risk to Public Health
SmPC	Summary of Product Characteristics
SPIDs	Summed Pain Intensity Differences
VAS	Visual Analogue Pain

Table of contents

1. Background Information

Referral of the matter to the CHMP

Vale Pharmaceuticals submitted to the United Kingdom a marketing authorisation application under the decentralised procedure (DCP) for paracetamol 500 mg and ibuprofen 150 mg fixed dose combination on 27 March 2015.

The application was submitted to the reference Member State (RMS): United Kingdom and the concerned Member States (CMS): Austria (AT), Germany (DE), Croatia (HR), Ireland (IE), Luxembourg (LU), France (FR), Belgium (BE), Netherlands (NL) , Portugal (PT) and Spain (ES).

The decentralised procedures UK/H/6034/001/DC, UK/H/6035/001/DC and UK/H/6176/001/DC started on 23 July 2015.

On day 210, major issues on efficacy and safety raised by DE, FR, NL and ES remained unresolved and were considered as a potential serious risk to public health; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by United Kingdom on 7 July 2016. The CMDh 60 day procedure was initiated on 22 August 2016.

Day 60 of the CMDh procedure was on 20 October 2016 and as no agreement could be reached the procedure was referred to the CHMP.

On 21 October 2016 the RMS United Kingdom therefore initiated a referral under Article 29(4) of Directive 2001/83/EC in view of the potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

The product is a fixed dose combination (FDC) of paracetamol (PAR) and ibuprofen (IBU), comprising in each tablet paracetamol 500 mg with ibuprofen 150 mg, for use from one to two tablets up to three times a day. The claimed indication is for use in adults aged over 18 years for “short-term symptomatic treatment of mild to moderate pain” for no more than 3 days.

Paracetamol has analgesic and antipyretic actions. The mechanism of action seems to be based on inhibition of the enzyme prostaglandin synthetase, but this does not explain the lack of anti-inflammatory actions. The benefit of paracetamol lies in the fact that some of the adverse effects characteristic of NSAIDs are completely or largely absent.

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and antipyretic activity. Its therapeutic effects, as an NSAID is thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

The properties of paracetamol and ibuprofen are all well-established. Both active substances are already widely used alone or in combination at the proposed doses for the current indication. Numerous proprietary products in various dose combinations of the active substances are available in many countries word-wide including the European Union.

The suggested FDC offers an alternative therapeutic option to opioid based combinations with all their implications regarding safety and addiction risks. This is significant as there are growing concerns relating to the safety issues associated with opioids such as codeine when used in addition to paracetamol.

During the decentralised procedure, several concerned member states (CMSs) raised a potential serious risk to public health (PSRPH) regarding the rationale of the FDC, the additional benefit for the new FDC compared to the mono-components and the safety profile of the new FDC. CMSs expressed some concerns regarding the demonstrated superiority being limited to one post-operative pain model (molar extraction) whilst the other pivotal study failed to demonstrate the superiority of the association in another pain model (arthroscopy), and that there was no evidence available of superiority in the treatment of mild pain.

All objecting CMSs requested a referral to CMDh during which their positions remained unchanged. In the absence of an agreement at CMDh, the matter was referred to CHMP for arbitration.

2.2. Clinical aspects

2.2.1. Clinical efficacy

Clinical studies

The application has been supported by four clinical studies involving a total of 909 subjects evaluated for efficacy. A summary of these studies can be found below.

Table 1. **Summary of pivotal clinical studies**

Study No.	FDC	Paracetamol	Ibuprofen	Placebo	Total
AFT-MX-1	40	43	39	-	122
AFT-MX-3	30	-	-	49	79
AFT-MX-6	110	111	112	75	408
AFT-MX-6E	77	73	75	75	300
Total	**257**	**227**	**226**	**199**	**909**

Study AFT-MX-1 was a phase III, pivotal study with a prospective, parallel group, double-blind comparison of the analgesic effect of a combination of paracetamol and ibuprofen, paracetamol alone, or ibuprofen alone in patients with postoperative pain. Its objective was to compare the analgesic effects and safety of paracetamol and ibuprofen combined (Combination) versus paracetamol alone or ibuprofen alone in adults with postoperative pain. The results showed that the mean time-adjusted area under the curves (AUCs) calculated from the visual analogue pain (VAS) scores in the Combination treatment group at rest (mean=22.3, standard error (SE)=3.2) and on activity (mean=28.4, SE=3.4) were significantly lower than the means in the paracetamol alone treatment group (at rest: mean=33.0 [SE=3.1]; on activity: mean=40.4 [SE=3.3]). These comparisons were statistically significant (p=0.007 on rest; p=0.006 on activity). The combination of paracetamol and

ibuprofen had greater analgesic efficacy than the same dose of paracetamol alone. The mean of time-adjusted AUCs calculated from the VAS pain scores in the Combination treatment group at rest (mean=22.3, SE=3.2) and on activity (mean=28.4, SE=3.4) were significantly lower than the means in the ibuprofen alone treatment group (at rest: mean=34.8 [SE=3.2]; on activity; mean=40.2 [SE=3.4]). These comparisons were statistically significant (p=0.003 on rest; p=0.007 on activity). The combination of paracetamol and ibuprofen had greater analgesic efficacy than the same dose of ibuprofen alone. The primary objective shows that the combination was statistically superior to the active substances individually. The secondary analyses show either no difference or in favour of the combination. The study was well conducted and showed that the efficacy of the combination is statistically superior to the efficacy of the mono-components on their own.

Study AFT-MX-3 was a dose response study and a double-blind, placebo-controlled, randomised, parallel group comparison of the effects of different paracetamol and ibuprofen combination doses and placebo in participants with pain from removal of 2-4 third molars. Its objective was to compare time-adjusted Summed Pain Intensity Differences (SPIDs) from baseline of the VAS pain intensity scores up to 24 hours after the first dose of study medication among the four treatment groups to determine the form of the dose-response relationship. The results showed that the means of time-adjusted SPIDs in placebo group (mean=6.63, SD=19.79) is significantly lower than either the one of Combination ¼ dose group (mean=19.25, SD=19.99), the Combination ½ dose group (mean=20.44, SD=20.78) or the Combination full dose group (mean=20.12, SD=18.01). The overall fixed effect of treatment was tested on this endpoint in the general linear model and the difference has reached the statistical significance (p=0.002). Following this, the pair-wise comparison between placebo group and each active treatment group was conducted and the difference has reached statistical significance (placebo versus Combination full dose P=0.004; placebo versus Combination ½ dose P=0.002; placebo versus. Combination ¼ dose P=0.002). In the study the treatment groups have all been shown to be statistically superior to placebo. They all seem numerically similar to each other; however no formal comparison between the treatment groups has been performed.

Study AFT-MX-3 was also a dose response study. The primary endpoint was met with a statistical significance of p=0.002. The study was not designed to allow comparison between individual doses and is in line with the EMA-Guideline [CPMP/ICH/378/95] for a dose-response study. However, it is noted that each dose (¼, ½ or full dose) of the FDC were superior to placebo with a statistical significance of $p < 0.01$. This supports that the two doses of the FDC (one or two tablets) can be tailored to the patients specific pain levels and deliver significant pain relief. In summary the FDC was superior to placebo (p=0.007) whereas the individual comparators could not demonstrate statistically significant superiority to placebo. Furthermore, it would appear that the pain (following key-hole surgery) in this study dissipated too quickly to allow enough time for discriminatory evaluation between treatment groups.

Study AFT-MX-4 was a phase II exploratory study with a double-blind, randomized, parallel group comparison of the effects of paracetamol and ibuprofen combined (Combination) with paracetamol, low and high dose ibuprofen on patients with pain from osteoarthritis of the knee, and a 12 month open label extension. Its objective was to compare the analgesic efficacy and clinical safety of Combination (paracetamol 500 mg and ibuprofen 150 mg) with the other 3 treatment groups (paracetamol 500 mg; low dose ibuprofen 150 mg; high dose ibuprofen 300 mg) in patients who have painful osteoarthritis of the knee. The results showed a mean improvement in the WOMAC VAS pain score from baseline to week 4 in the Combination treatment group (mean=25.1, SE=2.1) is greater than the mean improvement in the paracetamol alone group (mean=22.1, SE=2.3, p=0.168) and in the ibuprofen low dose group (mean=20.9, SE=2.2, p=0.085). The mean improvement in the WOMAC VAS pain score

from baseline to week 4 in the ibuprofen high dose treatment group (mean=26.4, SE=2.2) is greater than the mean improvement in the Combination group (mean=25.1, SE=2.1, p=0.638). The study has shown that in osteoarthritis pain, the combination is effective. AFT-MX-4 was only a pilot study to explore the effects of the FDC in comparison with either individual components or a double dose of ibuprofen. Despite the study included a small sample (N=33 in total), the trend was in favour of the FDC versus equivalent doses of the individual components and similar to high dose ibuprofen (2400 mg / day) which has both an analgesic and anti-inflammatory effect. In this respect the pilot study was entirely consistent with the remaining studies and gave an indication that likely efficacy is similar to high dose of NSAID but of course this would need to be confirmed in a larger pivotal study in chronic pain.

Study AFT-MX-6E was a phase III trial in another acute pain model (arthroscopy). This study is an acute pain study for mild-moderate pain since arthroscopy is a minor surgical procedure which results in little ongoing pain and in fact as discussed below pain dissipates rapidly. This phase 3 study was designed as a prospective, parallel-group, double-blind, placebo comparison of the clinical efficacy and safety of FDC (2 tablets, each tablet containing 500 mg paracetamol and 150 mg ibuprofen) versus its individual components (either 1000 mg paracetamol or 300 mg ibuprofen) and versus placebo in 300 patients suffering of moderate to severe pain due to post-arthroscopy surgery of the knee. The FDC provided more effective pain relief than placebo with a high level of statistical significance ($p < 0.01$). It should be noted though that comparison of either paracetamol 1000 mg or Ibuprofen 300 mg every six hours did not result in a SPID 0-24 hour statistically significantly superior to placebo ($p > 0.05$). There was still a trend towards the SPID 0-24 hour values for both paracetamol (49-71% greater) and ibuprofen (22-49% greater) being improved versus placebo. However these improvements were much less than those observed for the FDC (77-107%). The comparison between paracetamol and ibuprofen with FDC did not reach the significance level ($p > 0.05$). The reason for this was that the pain scores observed in the study were low over the 0-24 hour time period. The surgical procedure which utilised key-hole surgery caused minimal damage from the surgery and the pain scores decreased very rapidly. These sorts of pain studies require a significant level of pain in order to allow demonstration of statistical significant differences between analgesic treatments.

Study AFT –MX6 was another phase III, placebo-controlled, prospective, randomized, double-blind, parallel-design trial with a safety follow-up at day 30. Male and female participants aged 18 and 60 years undergoing surgical removal of least two impacted third molars were eligible for this study. The primary efficacy endpoint was the time-adjusted sum of pain intensity differences from baseline over a 48 hour period (SPID 48). Linear interpolation was used to estimate intermittent missing values. Rescue medication consumption was accounted for in the primary endpoint analysis by carrying forward the pre-rescue VAS pain score. According to the SPID 48, the FDC provided significantly greater pain relief than either mono-component ($p<0.001$). Median time to perceptible pain relief was significantly shorter for the FDC than ibuprofen and placebo ($p<0.05$) and non-significant for the comparison with paracetamol. Median time to meaningful pain relief was significantly shorter in the combination group than in all other groups ($p<0.05$). As only 41% of placebo patients achieved meaningful pain relief, it was not possible to calculate the median time meaningful pain relief in this sub-group.

No studies were performed on special population. However, data derived from the analysis of the above studies, lead to information regarding clinical safety in special (elderly) population (age > 65 years old) (see section of Clinical safety below).

Design and conduct of clinical studies

During the review process the methodological discussions centred around AFT-MX-1 regarding the lack of placebo as internal control. And on those grounds the superior efficacy of the FDC compared to each mono-component was deemed inconclusive. It is however noted by the CHMP that the data obtained in AFT-MX-6 which is a large phase III efficacy study in 408 subjects, are consistent with AFT-MX-1. This provides further insurance on the interpretation of the validity of the AFT-MX-1 results.

Another point of concern was related to the non-systematic patient pain assessments. Despite the non-systematic pain reporting of VAS assessments, the pain duration over which subjects assessed their pain was similar between the groups, thus enabling a standardised comparison. This was pre-specified for in the protocol design and statistical analysis plan which allow for interpolation of data to construct the VAS AUC values and is not considered by the CHMP to put into question the validity of the results.

The primary endpoint in the AFT-MX-1 study, time-adjusted AUC of VAS assessments made over 48 hours study period, provided an effective means of estimating the overall pain level over the study period and was not affected by differences in the duration between assessments, an approach which can be considered more rigorous as opposed to measurement over a single dose interval.

The applicant noted that FDC 500 mg / 150 mg involves active substances that are well established with recognised benefits and acceptable safety. The clinical studies submitted to support this application have been designed and performed in accordance with current CHMP guidelines[1].

Table 2. **Main Efficacy Studies and the Results for FDC PAR:IBU [3.3:1 or 1000:300mg]; Studies AFT-MX-1, AFT-MX-3, AFT-MX-6, and AFT-MX-6E)**

Study	Design	Pain model	N	Intervention (*n*)	Comparators (*n*)	Dosing	Primary Endpoint	Results
AFT-MX-6	Randomized, double-blind, placebo-controlled trial	Wisdom teeth extraction	408	FDC 325/97.5 (110)	Paracetamol (PARA) 325 mg *(111)* Ibuprofen (IBU) 97.5 mg *(112)* Placebo *(75)*	3 tablets First dose given postoperatively when VAS pain ≥ 40 mm. Subsequent doses administered q6h for 48 hours	Time-adjusted Sum of Pain Intensity Differences (SPID) from baseline over 48 hours – calculated as the area under the curve of pain intensity differences from baseline on 100 mm VAS. (Time-adjusted SPID48)	Combination superior to all comparators in terms of the primary endpoint Note: The dose is comparable to 500/150 as it is 97.5% of the full dose i.e. 1000 mg vs 975 mg Paracetamol and 300 mg vs 292.5 mg Ibuprofen. Bioequivalence studies between FDC 500/150 and FDC 325/97.5 demonstrated bioequivalence standards were met

AFT-MX-1	Randomized, double-blind, controlled trial	Wisdom teeth extraction	122	FDC 500/150 (*40*)	Paracetamol 500 mg (*43*) Ibuprofen 150 mg (*39*)	2 tablets First dose given pre-operatively. Subsequent doses administered q6h for 48 hours	Time-adjusted Area Under the Curve for VAS pain at rest and on activity over 48 hours (Time-adjusted AUC at rest, Time-adjusted AUC on activity)	Combination superior to monotherapies for primary endpoint.
AFT-MX-6E	Randomized, double-blind, placebo-controlled trial	Arthro-scopy	300	FDC 500/150 (*77*)	Paracetamol 500 mg (*73*) Ibuprofen 150 mg (*75*) Placebo (*75*)	2 tablets First dose given postoperatively when VAS pain ≥ 40 mm. Subsequent doses administered q6h for 24 hours	Time-adjusted SPID24	Combination superior to placebo for primary endpoint. Monotherapies were not superior to placebo for primary endpoint.
AFT-MX-3	Randomized, double-blind, controlled trial	Wisdom teeth extraction	159	FDC 500/150 (*30*) FDC 250/75 (*34*) FDC 125/37.5 (*46*)	Placebo (*49*)	2 tablets First dose given postoperatively when VAS pain ≥ 40 mm. Subsequent doses given q6h for 24 hours	Time-adjusted SPID24	The fixed-effect of treatment was tested on this endpoint in the general linear model and was highly significant (p=0.002). For the primary endpoint, all doses of the combination [including the claimed 1-2 tablet dose] were superior to placebo.

It was noted that FDC was unequivocally superior to placebo in terms of the time-adjusted SPID in both wisdom teeth extraction and arthroscopy pain models. The lack of superiority of the combination versus monotherapies in AFT-MX-6E is likely due to the rapid resolution of postoperative pain levels in this model. Patients in AFT-MX-6E met the entry criteria post-operatively if they experienced a VAS pain score ≥ 40 mm which is the level for moderate pain defined in the Pain Guideline [EMA/CHMP/970057/2011].

Clinical relevance analysis

The applicant analysed clinical relevance of the efficacy. The metric used for this analysis comparing the short-term analgesic efficacy of different drugs from numerous analgesic studies is the Number Needed to Treat (NNT) to achieve 'at least 50% maximum pain relief over 4 to 6 hours' versus placebo. Smaller NNT values indicate greater relative efficacy.

In order for the efficacy of an analgesic to be considered clinically relevant, an NNT of less 10 versus placebo must be obtained (Moore et al, 2015[2] – Cochrane review). Following this rationale, the clinical relevance of differences between different drugs and combinations can also be assessed. Considering data from the two placebo controlled studies, data from the primary endpoint of AFT-MX-6 and AFT-MX-6E studies (time-adjusted SPID) was used to assess the relative benefit of the proposed fixed dose combination over the monotherapy groups. In keeping with the Cochrane definition, subjects that did not record VAS pain scores for at least 4 hours were omitted from the analysis.

A total of 708 subjects were available for the analysis (408 from AFT-MX-6 and 300 from AFT-MX-6E). Of these, 611 recorded pain scores for at least 4 hours. The majority of the 97 subjects that did not record pain scores for this long were in the AFT-MX-6E (n=94). This again relates to the rapid dissipation of pain scores associated with this pain model (knee arthroscopy). Table 3 below, shows that the majority of subjects in the pooled FDC and IBU monotherapy groups achieved at least 50%

maximum pain relief (0.67 and 0.55, respectively). A smaller proportion of subjects in the paracetamol and placebo groups obtained at least 50% maximum pain relief. The comparison of the FDC and both mono-components yielded NNT values of less than 10 (NNT = 5.5 versus paracetamol and NNT = 8.7 versus ibuprofen), demonstrating that clinically relevant additional pain relief is provided by the combination over that provided by ibuprofen or paracetamol alone.

Table 3. **NNT comparison between the FDC and IBU or PAR monotherapy of AFT-MX-6 (wisdom teeth extraction) and AFT-MX-6E (arthroscopy) Studies.**

	Number of Subjects with		Total	Proportion of subjects with at least 50% maximum pain relief (P)	Number Needed to Treat (NNT)	
Drug	At least 50% maximum pain relief	Less than 50% maximum pain relief			Versus. Placebo**	Combo versus comparators ***
Combination*	111	55	166	0.67	2.7	-
Ibuprofen	93	75	168	0.55	4.0	**8.7**
Paracetamol	77	81	158	0.49	5.4	**5.5**
Placebo	36	83	119	0.30	-	**2.7**
Total	**317**	**294**	**611**			

** FDC/Maxigesic or Maxigesic 325 [Paracetamol 975mg + Ibuprofen 292.5mg]*
*** NNT=1/(P_{drug}-$P_{Placebo}$)*
**** NNT=1/($P_{Combination}$-P_{drug}). Note the values are less than 10 consistent with a clinically meaningful level of analgesic difference as defined by the Cochrane Review*
Note: *AFT-MX-3 was not included in this analysis as the study did not incorporate mono-component (Ibuprofen and/or Paracetamol) treatment groups. AFT-MX-1 was not included in the analysis as the first dose of study medication was administered prior to surgery and no baseline VAS pain could be established.*

Analysis of multiple dose data pooled from more than one study

The applicant also performed an analysis of the data pooled from the studies AFTMX-6, AFT-MX-1, AFT-MX-3, and AFT-MX-6E. These were four randomized, multiple dose, clinical studies in two models of acute pain. Despite differences in pain model (wisdom teeth extraction versus knee arthroscopy), age group, small differences in duration (24 versus 48 hours), timing of the first dose (pre-operative and post-operative) and VAS assessments, the VAS data from each of these studies can be pooled to permit the analysis of the efficacy of the fixed dose combination and comparable doses of each monotherapy and placebo in acute pain in general. For the purpose of this meta-analysis, data from clinical trials conducted with a similar FDC (FDC 975 mg/292.5 mg, AFT-MX-6) as well as the FDC 1000 mg /300 mg (AFT-MX-1, AFT-MX-3, and AFT-MX-6E) were pooled together. Studies concerning both FDC constitute the primary source of efficacy information in this summary. Pooling data from both combinations is justified by the fact that the cumulative dose of both active ingredients from the FDC 975 mg/292.5 mg is 97.5% of that of the related product FDC 1000 mg/300 mg. Therefore, for the purposes of a meta-analysis of efficacy, these two products can be considered similar when taken at full doses.

A total of 1002 patients were enrolled in the acute clinical efficacy studies of FDC (AFT-MX-6, AFT-MX-1, AFT-MX-3 AFT-MX-6E). A total of 93 subjects either did not return their diaries (n=13) so VAS assessments could not be verified, or took smaller dose (n=80). These participants were omitted from

the pooled efficacy population to maintain the comparison across full doses of the combination and monotherapy comparators. Consequently, the pooled efficacy population comprises a total of 909 subjects.

AUC results: Initial inspection of the general liner model revealed that pain model (wisdom teeth extraction and knee arthroscopy) was not a significant factor. Consequently, the final model included only study number as factor, which was also a non-significant factor (p=0.203). The mean time-adjusted AUC of VAS pain assessments are presented in Table 4, below. Pair wise comparisons revealed that the mean AUC was significantly lower for the pooled FDC group than the pooled ibuprofen (p=0.020), paracetamol (p<0.001) or placebo (p<0.001) groups.

Table 4. **Mean (95% CI) Time-adjusted AUC of VAS pain scores over 24-48 hours for pooled full dose groups and PBO; Studies AFTMX-6, AFT-MX-1, AFT-MX-3, and AFT-MX-6E.**

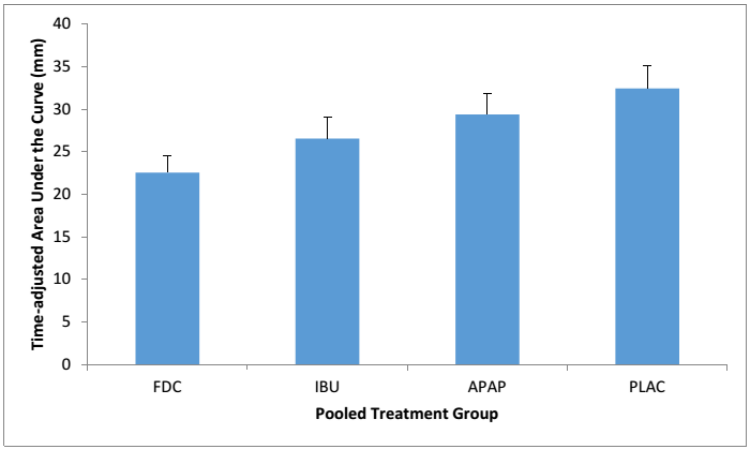

Table 5. **Pair-wise comparisons of AUC between pooled FDC and pooled comparator groups. Studies AFTMX-6, AFT-MX-1, AFT-MX-3, and AFT-MX-6E**

Pairwise Comparisons					
Comparison		Mean Difference	Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
FDC	Ibuprofen	-3.992	0.015	-7.199	-0.785
	Paracetamol	-6.851	0.000	-10.056	-3.646
	Placebo	-10.22	0.000	-13.095	-6.726

Rationale for its first line use in the claimed indication

Both paracetamol and ibuprofen doses are limited by safety concerns. Paracetamol dose cannot be increased over and above the maximum recommended doses due to concerns of liver toxicity. Ibuprofen doses along with all NSAIDs are recommended to be minimised under current EMA guideline [EMEA/CHMP/410051/2006][1]. The CHMP agreed that this FDC allows minimising the doses of the monocomponents paracetamol and ibuprofen.

In response to the request for justification of the first line therapy for “short term symptomatic treatment of mild to moderate pain” the applicant stated that this FDC achieves greater analgesia whilst minimising doses of the monocomponents. This is supported by both pivotal study and by an NNT analysis. The CHMP agreed with this rationale, as much as proven by pivotal study showing superiority over single components in “acute somatic pain” but not for chronic pain or visceral pain.

Recommended dose, maximum dose and dose ratio

The MAA presented the maximal daily doses approved currently in EU countries.

The proposed dose of 3000 mg/900 mg is within the dose range studied i.e. 4000 mg/1200 mg, and improved efficacy is shown versus individual components at both 3000 mg/900 mg and 4000 mg/1200 mg strengths.

The specific efficacy of ibuprofen 900 mg has been extensively discussed throughout this procedure. In addition to the clinical data submitted, data presented by Derry et al. 2009[3] in a review of 49 studies supports the assertion that ibuprofen is effective in doses between 50 – 400 mg, in acute pain. Hence lowering the dose of ibuprofen to the amount given in this combination (150 mg to 300 mg/dose) is consistent with available literature data in terms of efficacy.

In comparison to lower dose ratio combinations, a 3.33:1 ratio provides superior analgesia over both monotherapies. However this does emphasise that the data for this FDC supports an optimal ratio for safety and efficacy and that not all ratios of paracetamol/ibuprofen are directly comparable since they cannot all show superiority of the FDC against the mono-components. Despite the claimed dose posology is every 6 hours, the analgesic effects of the combination are still present in appreciable amounts beyond 6 hours after administration.

Conclusions on clinical efficacy

The applicant has also conducted a meta-analysis across the four constituent studies to further justify the benefit of the FDC over its mono-components. The standardised measure of efficacy is the time-adjusted AUC of VAS pain scores and the applicant has suitably justified that, although this was not the primary endpoint in all studies, the relevant information is available in all studies. The pooled analysis shows that the FDC is statistically superior to each of the mono-components. The previously highlighted shortcomings in the clinical trials are not an object to major objection to the CHMP. Overall, the submitted clinical studies show that all components of the FDC were involved in its effectiveness. In particular, ibuprofen was shown to contribute to the therapeutic effect. This is consistent with the requirements set out in the CHMP guideline on clinical development of FDC medicinal products (EMEA/CHMP/281825/15).

Several CHMP members have expressed some concerns regarding the demonstrated superiority being limited to one post-operative pain model (molar extraction) whilst the other pivotal study failed to demonstrate the superiority of the association in another pain model (arthroscopy), and that there was no evidence available of superiority in the treatment of mild pain. For moderate pain, the benefits of the relatively small amount of ibuprofen were also not robustly shown.

The CHMP took into consideration these concerns but concluded that overall the efficacy of the combination for the short duration of use of 3 days for the symptomatic treatment of mild to moderate pain has been demonstrated.

2.2.2. Clinical safety

Paracetamol and ibuprofen are two analgesic compounds with long histories of clinical use and both have been shown to be safe and well tolerated at maximum recommended daily doses. The dose strengths used in the proposed fixed dose combination are well within the recommended dose range, particularly with regards to the dose of ibuprofen. The safety concerns by the member states were on the impact of the combination in different age-groups, particularly in elderly patients, and also on the off label of prolonged use.

Patient exposure in clinical trials

Overall, 312 of 955 (33%) of patients have experienced at least one AE during the double-blind treatment phases of AFT-MX-1, AFT-MX-3, AFT-MX-4, AFT-MX-6E and AFT-MX-6. The proportion of patients in the pooled FDC and pooled ibuprofen monotherapy groups that experienced at least one AE were comparable (29% and 28%, respectively). The same is true for the pooled paracetamol and placebo groups (both 37%).

Across the 5 clinical efficacy studies of the FDC, 698 AEs were reported, 12 of which could not be coded according to the Trial Phase due to unknown dates (11 in AFT-MX-1 and 1 in AFT-MX-6E).

587 of the 698 (88%) AEs occurred during treatment (blinded or open-label). As stated previously these are most relevant AEs to discussions of the safety and tolerability of the proposed fixed dose combination and indication (short term [no more than three days] treatment of acute pain).

Regarding the proposed short term use, the observed rate of AEs is no worse than placebo or maximum daily doses of the individual components: the Odds of experiencing at least one AE with the combination is similar to that of the either mono-component for each comparison.

No death or serious adverse events attributable to the active substances were seen in these trials.

The safety and tolerability of the FDC is supported by the post-marketing data collected from 186 million patients in the UK and Italy which have used the FDC and 6.08 million patients in the rest of the world (non EU countries), where only 3 AEs were reported for the population including the elderly population from 2009 to 2016. Out of the 3 AEs – only one AE (epistaxis) was concluded as probably related to the FDC, however this is a common adverse reaction to any NSAID-containing medicine.

The pharmacokinetics of either medicinal product is not affected by the presence of the other, as the metabolic pathways are different. As a result no drug-drug interactions are expected, and the combination is considered safe in that respect.

Post-marketing experience

The post marketing experience for the product in the UK and worldwide is also supportive of its safety as the two separate components are widely co-prescribed.

Moreover, this FDC has been in use for a number of years in non EU markets (Australia and New Zealand). A total of 89 million tablets have been sold globally, with more than 15 million tablets in the EU without any unexpected safety signals.

The post-marketing experience for the product in the UK and worldwide is also supportive of its safety as the two separate components are widely co-prescribed. Furthermore, approximately 1.86 million

patients in the UK and Italy have used the FDC and more than 6.08 million patients in the rest of the world (excluding the EU) with three minimal AEs and only one Serious Adverse Event reported throughout the last 7 years (2009-2016). A summary of the AEs included in the periodic safety update report (PSUR). The PSUR would undoubtedly cover a range of ages and uses based upon real in market experience. Therefore the risk for prolonged use of the fixed dose combination and paracetamol or ibuprofen alone should have a similar benefit-risk profile.

Furthermore in a study population (de Vries el al. 2010)[4] which included 1.2 million patients, whose aim was to evaluate and compare the risk of specific safety outcomes in patients prescribed ibuprofen and paracetamol concomitantly with those in patients prescribed ibuprofen or paracetamol alone, concluded that the known risk of the safety outcomes examined does not appear to be modified by concomitant use of ibuprofen and paracetamol compared with the mono-components alone. The safety outcomes evaluated were upper gastrointestinal events, myocardial infarction, stroke, renal failure (excluding chronic), congestive heart failure, intentional or accidental overdose, suicidal behaviour and mortality.

The important safety risks associated with prolonged use of paracetamol and ibuprofen are well known and are hepatotoxicity, peptic ulceration and gastrointestinal bleeding, nephrotoxicity, cardiac, cardiovascular and cerebrovascular effects. The applicant has provided a comprehensive review of the safety data both from the submitted studies and from overall pooled study data including the exposure of the combination in elderly patients. The applicant presented literature search strategy. Based on clinical data provided by the applicant, no new safety issues have been identified. The incidence of adverse events is as expected and most commonly involves the gastrointestinal tract. More importantly this is consistent with the post marketing experience of the use of the combination both world-wide and in the countries within the EU.

Safety in elderly

Cumulatively, in the 5 studies (AFT-MX-1, AFT-MX-3, AFT-MX-4, AFT-MX-6E and AFT-MX-6, 27), 955 patients participated in total. A 3% of all patients were aged 65 years and over. The distribution of these 27 elderly patients according to study and treatment group is summarized below. All elderly patients were enrolled in studies AFT-MX-6E and AFT-MX-4, which is a reflection of the pain model used in both studies (post arthroscopic surgery pain and osteoarthritis pain, respectively).

Table 6. **Distribution of elderly patients by Study and Treatment Group**

Study	Treatment Group					Grand Total
	FDC	IBU Low	PARA	PLAC	IBU High	
	N=270	N=239	N=239	N=199	N=8	N=955
AFT-MX-4	4	2			3	9
AFT-MX-6E	3	4	5	6		18
Grand Total	**7**	**6**	**5**	**6**	**3**	**27**
%	**2.6%**	**2.5%**	**2.1%**	**3%**	**37%**	**3%**

Overall, AEs reported by the 27 elderly patients during the double-blind phases of AFT-MX-4 and AFT-MX-6E reveal that the FDC is well tolerated in this subset of patients as it is in the pooled population of all 5 clinically efficacy studies.

Conclusions on clinical safety

In conclusion, the safety outcomes examined were consistent, both in terms of frequency and severity of adverse events between the concomitant use of the FDC compared with the use of paracetamol or ibuprofen alone at similar doses.

During the CHMP discussion, members expressed divergent views based mainly on the potential for increased risks of rare but severe adverse events due to overtreatment, uncertainty in some treatment populations, that the expected benefits are not considered sufficient to accept these increased risks and that no evidence was provided to support the need of this product or its first-line use.

The CHMP took these comments into account, and considered that with the additional amendments to the product information for the restriction of use to maximum of 3 days, and the additional data provided for special populations including the elderly, that the overall safety of this FDC to be acceptable in the indication for the short-term symptomatic treatment of mild to moderate pain.

2.2.3. Justification of the FDC rationale

The applicant argued that improved and rapid relief of acute pain results in longer pain relief. The applicant discussed the results from several studies (AFT-MX-1, Merry et al. 2010[5], Mehlisch et al. 2010[6], and Mehlisch et al. 2010b[7], Moore et al. 2015[2]) in support of the argument that the FDC limits the re-medication need on patients who seek additional analgesia as compared to respective paracetamol or ibuprofen monotherapies. Data from the pivotal study AFT-MX-6, showed that 43-52% of patients treated with either paracetamol or ibuprofen alone sought additional pain relief, evidenced through using rescue medication.

Another point of consideration is that the FDC is an alternative therapeutic option to opioid based combinations in the view of growing concerns regarding to the safety issues associated with opioids such as codeine when used in combination with paracetamol. This FDC also minimises some safety risks due to overdosing of ibuprofen by minimising its effective dose, in line with EMA guideline [EMEA/CHMP/410051/2006][1].

Furthermore, in terms of safety there is supportive data to exclude any additive adverse effects on gastric erosions and bleeding when paracetamol is added to ibuprofen in the ratio of 3.3:1, and the efficacy provided by the fixed dose combination over either of the individual components does show any decreased tolerability/safety.

Finally, according to IMS data, there were more than 5 million co-prescriptions in the USA and UK in the 12 months to the end of 2007 and that can be explained as a need for this combination is recognised by healthcare professionals.

The CHMP accepted this justification by the applicant and concluded that there is a clinical need for this fixed dose combination in short term treatment of acute pain.

2.2.4. Risk management

This medicinal product is already authorised during the first and second waves of the decentralised procedure as 'prescription only' medicine in many EU countries.

All the risks associated with prolonged use (i.e. outside the terms of the marketing authorisation) have been identified as safety concern in the current risk management plan. These risks are well known and are controlled by routine pharmacovigilance practices which CHMP has endorsed.

In order to minimise the risk associated with prolonged use, the CHMP recommended to limit the indication to a short term use (maximum for 3 days). Instructions in the posology section, warnings for the duration of use and safety information on special populations, including elderly, hepatic and renal impaired patients were updated accordingly in the product information.

As the proposed fixed dose combination is recommended to be used for no more than 3 days, the potential for prolonged use is largely mitigated. Furthermore, the extensive post-marketing experience indicates the potential for prolonged use is unlikely to materialise.

As additional risk minimisation measure the Member States should take into consideration the adequacy of the pack size in order to not exceed the maximum daily recommended dose of 3000 mg / 900 mg paracetamol/ibuprofen (6 tablets) for maximal duration of three days.

A risk management plan has been submitted in line with the above.

3. Benefit-risk balance

Paracetamol and ibuprofen are two analgesic compounds with long histories of clinical use and both have been shown to be safe and well tolerated at maximum recommended daily doses. The dose strengths used in the proposed fixed dose combination are well within the recommended dose range particularly with regards to the dose of ibuprofen.

During the review process the superior efficacy of the fixed dose combination were compared to each mono-component. The data obtained in AFT-MX-1 is reinforced by the large phase III efficacy study AFT-MX-6. The results from AFT-MX-6 are consistent with AFT-MX-1 which in fact further reinforces the validity of the AFT-MX-1 results. Despite the non-systematic pain reporting of VAS assessments, the pain duration over which subjects assessed their pain was similar between the groups, thus enabling a standardised comparison. In conclusion, the fixed-dose combination was considered as clinically superior in the clinical setting, based on studies AFT-MX-1 and AFT-MX-6, taking under consideration all the limitations of lack of placebo as internal control and the non-systematic patient pain assessments.

With regards the safety of this fixed dose combination, following the assessment of the data in the clinical trials as well as post-marketing experience, including the PSURs submitted on the mono-components, including an extensive search of the published literature, the CHMP concluded that the known safety outcomes with the use of the monocomponents alone are similar with the concomitant use of Ibuprofen and Paracetamol for similar doses. The safety outcomes evaluated were upper gastrointestinal events, myocardial infarction, stroke, renal failure (excluding chronic), congestive heart failure, intentional or accidental overdose, suicidal behaviour and mortality.

In summary, having assessed all the available data in support of the use of this combination in the short term treatment of pain, the CHMP concluded that the data demonstrated that the use of the combination of paracetamol and ibuprofen at the given doses is safe and effective in the intended indication, duration of use (limited to 3 days maximum) and population, including the elderly is more efficacious than the monocomponents used alone with an acceptable level of safety.

In particular, this fixed-dose combination does not have the risks of abuse and misuse of opioids. In the absence of this fixed dose combination the rescue remedy for the pain is resulting in use of opioids, instead. The use of the fixed combination will give time to both patients and physicians before an opioid containing product will be used.

Having considered all the data submitted by the applicant, the CHMP considered that the benefit-risk balance was adequately demonstrated. The CHMP was of the opinion that the benefit-risk balance of Paracetamol / ibuprofen 500 mg / 150 mg film coated tablets and associated names fixed dose combination is considered to be favourable when used in accordance with the terms of the product information.

4. Grounds for Opinion

Whereas,

- The Committee considered the notification of the referral initiated by the United Kingdom under Article 29(4) of Directive 2001/83/EC on the basis that France, Germany, Spain and The Netherlands considered that the granting of the marketing authorisation would constitute a potential serious risk to public health.

- The Committee reviewed all the data submitted by the applicant in support of the efficacy of Paracetamol/ibuprofen 500 mg / 150 mg film coated tablets and associated names fixed dose combination in short-term symptomatic treatment of mild to moderate pain.

- The Committee is of the opinion that the available data is supportive of the efficacy of Paracetamol/ibuprofen 500 mg / 150 mg film coated tablets and associated names fixed dose combination in short-term symptomatic treatment of mild to moderate pain.

- The Committee is also of the opinion that adequate information in order to minimise any risk of use outside of the recommended duration of use of maximum of 3 days has been included in the proposed product information and in the updated risk management plan, in this regard. In addition the safety information on special populations, including elderly, hepatic and renal impaired patients was strengthened to reflect the warnings related to mono-component use.

- The Committee concluded by majority that the benefit risk balance of this medicinal product in the short-term symptomatic treatment of mild to moderate pain is favourable.

Having considered the above, the CHMP has recommended by majority the granting of the marketing authorisation for which the summary of product characteristics, labelling and package leaflet was

amended following the final version achieved during the Coordination group procedure as mentioned in Annex III for Paracetamol/ibuprofen 500 mg / 150 mg film coated tablets and associated names fixed dose combination.

5. Enclosures

1. Divergent positions

Enclosure 1

Divergent position(s)

Article 29(4) of Directive 2001/83/EC

EMEA/H/A-29(4)/1447

Paracetamol/ibuprofen 500 mg / 150 mg Film-coated tablets and associated names

paracetamol/ibuprofen 500mg/150mg

Divergent statement

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Paracetamol/ibuprofen 500 mg / 150 mg Film-coated tablets and associated names indicated in the short-term symptomatic treatment of mild to moderate pain. The applicant for this medicinal product is Vale Pharmaceuticals Limited.

The reasons for divergent opinion are the following:

1. Increased risks of rare but severe adverse events:
    - The combined use of paracetamol and ibuprofen will associate their respective risks. These risks are rare, but can be severe.
    - Uncertainty regarding a synergistic risk of blood loss, as highlighted by one publication (Doherty et al 2011), and of increased risks of hepatotoxicity.
    - Uncertainty in some populations: elderly patients, pregnant women.
    - The current indications contradict the general clinical guidelines which recommend to use the lowest effective dose for the shortest time.
2. The expected benefits are not considered sufficient to accept these increased risks:
    - The superiority over the mono-components was not robustly demonstrated, and limited to one post-operative pain model (molar extraction).
    - Another pivot study failed to demonstrate the superiority of the association in another pain model (arthroscopy).
    - Particularly, there was no evidence available of superiority in the treatment of mild pain. For moderate pain, the benefits of the relatively small amount of ibuprofen were also not robustly shown.
    - The clinical relevance of the alleged faster onset of the association is contested.
    - The evidence did not consider all available evidence. Particularly, contradictory publications were ignored without any satisfactory justification.
3. No evidence was provided to support the need of this product or its first-line use:
    - Paracetamol and ibuprofen are easily accessible as individual components.
    - The association deprives patients from the flexibility to stop one of the molecules when both are not required anymore.
    - The reported Numbers Necessary to Treat (8.7 vs. ibuprofen and 5.5 vs. paracetamol) are not considered sufficient to warrant a first-line use, which could lead to overtreatment.

Overall, for these reasons, we consider that the benefit/risk ratio is negative for Paracetamol/ibuprofen 500 mg / 150 mg Film-coated tablets and associated names in the claimed indication.

CHMP members expressing a divergent opinion:

Concepcion Prieto Yerro (ES)	18 May 2017	Signature: .....
Sol Ruiz (Co-opted member)	18 May 2017	Signature: .....
Alexandre Moreau (FR)	18 May 2017	Signature: .....
Johann Lodewijk Hillege (NL)	18 May 2017	Signature: .....

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