

## **Annex II**

### **Scientific conclusions**

## Scientific conclusions

Vale Pharmaceuticals submitted to the United Kingdom an application under the decentralised procedure (DCP) for Paracetamol 500mg and Ibuprofen 150mg fixed dose combination on 27 March 2015.

The reference Member State (RMS) is the 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. Major issues on efficacy and safety raised by several CMS 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(1) of Directive 2001/83/EC. As at the CMDh procedure no agreement could be reached the procedure was referred to the CHMP.

On 21 October 2016 the RMS United Kingdom therefore triggered a referral under Article 29(4) of Directive 2001/83/EC as these issues were considered to be a potential serious risk to public health.

The main issues were the basis of the referral to CHMP which were that the rationale of the fixed dose combination is not considered justified, the additional benefit for this new fixed dose combination compared to the mono-components has not been demonstrated and that an acceptable safety profile of the new fixed-dose combination has not been shown.

### Clinical efficacy

The following main studies were submitted by the applicant in support of the marketing authorisation application.

*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 versus paracetamol alone or ibuprofen alone in adults with postoperative pain. The results showed that the combination of paracetamol and ibuprofen had greater analgesic efficacy than the same dose of ibuprofen alone. The primary objective showed that the combination was statistically superior to the active substances individually. The secondary analyses showed either no difference or in favour of the combination.

*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 Visual Analogue Pain (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, standard deviation (SD)=20.78) or the Combination full dose group (mean=20.12, SD=18.01). In the study the active substances have all been shown to be statistically superior to placebo. They all seem numerically similar to each other; however no formal comparison between the active substances was performed.

*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 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 500mg and ibuprofen 150 mg) with the other 3 treatment groups (paracetamol 500 mg; low dose ibuprofen 150 mg; high dose ibuprofen 300mg) in patients who have painful osteoarthritis of the knee. This phase II exploratory study has shown that in osteoarthritis pain, the combination is effective.

*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 III study was designed as a prospective, parallel-group, double-blind, placebo comparison of the clinical efficacy and safety of fixed dose combination (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.

*Study AFT –MX6* was another phase III, placebo-controlled, prospective, randomised, 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. 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. The results showed that the combination provided significantly greater pain relief than either mono-component ( $p < 0.001$ ). Median time to perceptible pain relief was significantly shorter for the combination than ibuprofen and placebo ( $p < 0.05$ ) and non-significant for the comparison with paracetamol.

CHMP members have expressed some concerns regarding the demonstrated superiority being limited to one post-operative pain model (molar extraction), that another pivot 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 noted the concerns by these members, but agreed that overall the efficacy of the combination for the short duration of use of 3 days has been demonstrated.

#### 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.

Clinical trials with the fixed dose combination have also not indicated any other undesirable effects other than those known for paracetamol alone or ibuprofen alone). The applicant noted also the PSUR reports which cover over 89 million tablets of market use have not suggested any additional or unexpected risks. The PSURs 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 risk/benefit profile.

Furthermore in a study population 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. In conclusion, the safety outcomes examined were consistent in the concomitant use of ibuprofen and paracetamol compared with paracetamol or ibuprofen alone.

The important safety risk 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. The CHMP requested that specifically for the special populations of hepatic and renal impaired patients the warnings related to paracetamol use are all in line with the warnings existing in the mono-component's product information, for completeness of the safety information.

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.

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 fixed-dose combination to be acceptable in the indication for the short-term symptomatic treatment of mild to moderate pain.

#### Rationale for use of the fixed dose combination ratio

The rationale of the applicant presented the need for the fixed dose combination in short term treatment of acute pain was presented to the CHMP.

Firstly, the two active substances in this fixed dose combination are supported by extensive published and regulatory evidence and history of efficacy and safety.

Secondly the ratio of paracetamol to ibuprofen (3.3:1) is of paramount importance as there is a distinct additive effect in both acute and chronic pain models, which is lost if the ratio is decreased. Ibuprofen is the safest of the NSAIDs and is therefore an optimal choice.

Thirdly, there is a medical need for a new fixed dose combination analgesic that does not contain an opioid component for relief of acute pain. It is noted that there is significant use of opioid combinations in the EU. A variety of reports show that the addition of codeine to common non-opioid analgesics provides additional pain relief at the cost of tolerability, compromising the benefit-risk ratio. Furthermore, for this substance combination, there is no interference with their individual metabolic pathways, and they also act through different pharmacological pathways.

Finally 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.

The fixed dose combination avoids the need to move to opioids 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. The proposed combination therefore offers an alternative therapeutic option to such opioid based combinations. It is worth noting that the indication being sought is for short term (3 days) exposure.

The CHMP accepted this justification by the applicant for the need for the fixed dose combination in short term treatment of acute pain is acceptable for the several reasons.

#### 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 have been identified as safety concerns in the current risk management plan. These risks are well known and are controlled by routine pharmacovigilance practices which CHMP has endorsed.

The short term use (max for 3 days) of this fixed dose combination has been recommended by the CHMP and accepted by the applicant. Appropriately, instructions in the posology section and warnings for the duration of use were provided in the product information.

The applicant noted that prolonged use exceeding the recommended three-day period may be only at the discretion and close supervision of a healthcare professional, who should ensure the rational and responsible use of the medicine and considered benefits versus risks and review the patient to assess for effect, side-effects and the need to continue. 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. The extensive post-marketing experience in countries outside EU indicates the potential for prolonged use is unlikely to materialise. Therefore such a potential has virtually no impact on the benefit-risk status of the medicinal product.

In the potential of medication without the supervision by healthcare potential additional risk minimisation measure would be the restriction of the pack size in order not to exceed the maximum daily recommended dose of 3000 / 900 mg paracetamol/ibuprofen (6 tablets) for maximal duration of three days.

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

#### **Benefit-risk assessment**

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.

With regards the safety of this fixed dose combination, following the assessment of the data in the clinical trials as well as the PSUR and an extensive search of the published literature concluded that the known safety outcomes are expected 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. When comparing with past users, for most safety outcomes, current users of concomitant paracetamol and ibuprofen had relative rates between those for current users of ibuprofen alone and paracetamol alone. In conclusion, the known risk of the safety outcomes examined does not appear to be modified by concomitant use of ibuprofen and paracetamol compared with paracetamol or ibuprofen alone.

The CHMP assessed the available data and the additional supportive data from literature to support the use of this combination in the short term treatment of pain. Overall, 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 and population, including the elderly. In particular, the combination does not have the risks of abuse and misuse of opioids. In 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.

The CHMP also recommended the short term use (max for 3 days) of this fixed dose combination. Instructions in the posology section and warnings for the duration of use were provided in the product information.

#### **Overall benefit-risk balance**

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.

#### ***Grounds for the CHMP 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. (see Annex I).