LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Comboval
(paracetamol, ibuprofen)

SE/H/2093/001/DC

This module reflects the scientific discussion for the approval of Comboval. The procedure was finalised on 2021-05-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Comboval, 10 mg/ml +3 mg/ml, Solution for infusion.

The active substances are paracetamol and ibuprofen. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Comboval (SE/H/2093/01/DC), with paracetamol and ibuprofen in strengths of 10 mg/ml and 3 mg/ml respectively, solution for IV infusion, is submitted according to Article 8(3) of Directive 2001/83/EC (Known active substances). The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS): DK, FI, IS, NO.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

The non-clinical file is mainly based on literature data and non-clinical *in vivo* studies in the rat and the rabbit, and two *ex vivo* studies in human whole blood. Paracetamol and Ibuprofen are well known substances with long histories of safe clinical use throughout the world and the pharmacology, pharmacokinetics and the toxicology based on literature review is, thus, appropriate.

Pharmacology

Paracetamol

Paracetamol is an analgesic and antipyretic agent commonly used for the relief of fever, headaches, and other minor aches and pains. Paracetamol reduces the production of prostaglandins, but it has relatively little of the anti-inflammatory activity.

Ibuprofen

Ibuprofen is believed to work by inhibiting cyclo-oxygenase (COX), thus inhibiting prostaglandin synthesis. The pharmacological activities of Ibuprofen are due to COX2 inhibition, while its unwanted side effects on platelet aggregation and the GI mucosa are due to COX-1 inhibition.

Pharmacokinetics

Both paracetamol and ibuprofen are metabolised primarily by the liver. Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation Paracetamol metabolites include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liver damage.

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one drug affects the metabolism of the other drug. AFT Pharmaceuticals Ltd. has reported in a study using human liver enzymes, that there was no inhibition of CYP enzymes when the drugs were applied in combination.

Toxicology

Single and repeated dose toxicity

The primary adverse effects on the function of key organ systems associated with ibuprofen involve the GI tract (irritation and bleeding), kidney (interstitial nephritis, renal papillary necrosis) and cardiovascular system (hypertension, myocardial infarction, stroke, thrombosis) and those associated with paracetamol involve the liver (hepatocellular necrosis).

In addition to literature data the applicant provided *in vivo* and *in vitro* studies showing that co administration of paracetamol and ibuprofen did not increase the risk of gastrointestinal or renal toxicity, has little potential to produce local irritation when administered intravenously, and did not cause additional hemolysis, plasma protein flocculation/precipitation or platelet aggregation.

Genotoxicity and Carcinogenicity

Ibuprofen is negative for mutagenic potential according to Ame's assay and negative in a chromosome aberration assay in human lymphocytes, but positive in a mouse bone marrow micronucleus assay. Carcinogenic studies of ibuprofen in mice and rats have been performed with no increase in tumour incidence.

Reproductive and developmental toxicity

Ibuprofen administered to pregnant rats, mice or rabbits during the period of organogenesis, did not affect the foetal development in either species.

Paracetamol does not present a teratogenic risk to humans at doses associated with severe maternal toxicity nor affect reproductive performance of mice in a continuous breeding protocol, although growth and birth weights were reduced. Sperm abnormalities have been observed in mice

(International Agency for Research on Cancer, 1999).

Environmental Risk Assessment (ERA)
An environmental risk assessment based on available literature in accordance with the relevant guidelines was performed. As the PECsurface water value obtained is higher than the trigger value of 0.01 µg/L for both paracetamol and ibuprofen, a Phase II environmental fate and effect analysis was done.

Summary of main study results

Substance (INN/Invented Name): Paracetamol					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log Kow	Langdon et al, 2010; TOXNET HSDB, 2018, which cites Sangster J; LOGKOW Database; Brun et al, 2006	0.46-0.49			Potential PBT (N)
PBT-assessment					
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	2.0 (default)	µg/L			> 0.01 threshold Yes
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	EPISuite	Log K_{oc} =1.79			21 (ref.; Toxnet HSDB, 2015, ECHA)
Ready Biodegradability Test	OECD 301	57%			The degradation rate of sodium benzoate (manometric test) was in line with OECD 301F criteria.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ =3.1 Day $DT_{50,\ sediment}$ =N/A $DT_{50,\ whole\ system}$ =3.1 Day			(e.g. not required if readily biodegradable)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Species*	OECD 201	EC_{50} IC_{25}	134 32	mg/L µg/L	*Scenedesmus subspicatus* *Selanastrum capricornutu*

	Environment Canada standard method				
Daphnia sp. Reproduction Test	OECD 211	NOEC	5.72	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	Henschel et al. 1997	EC_{50} (mortality)	378	mg/L	Zebra fish *(Brachydanio rerio)*
Activated Sludge, digital imaging on algal, cyanobacterial and bacterial biomass	Lawrence et al. 2012	NOEC	5	µg/L	

N/A=Not Analysed

Substance (INN/Invented Name): Ibuprofen					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	Langdon et al, 2010; TOXNET HSDB, 2018, which cites Avdeef A, J Pharm Sci, 1997; Williams et al, 2009, which cites Syracuse Research Corporation	3.5-3.97			Potential PBT (N)
PBT-assessment					
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	6.0 (default)	µg/L			> 0.01 threshold Yes
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	EPISuite	Log K_{oc} =2.59			
Ready Biodegradability Test	OECD 301	68% (mineralized)			Parent compound and metabolites decreased to <2% of the spiked amount.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	Comparable way to OECD 308	$DT_{90,\ water}$ = 13 Days $DT_{90,\ sediment}$ = N/A $DT_{90,\ whole\ system}$ = <6 Days % shifting to sediment =			(e.g. not required if readily biodegradable)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	Environment Canada test protocols Cleuvers, 2006	NOEC NOEC	10 32	µg/L mg/L	*Selanastrum capricornutum*

					Scenedesmus subspicatus
Daphnia sp. Reproduction Test	Brun et al. 2006	IC_{25}	>32	µg/L	
Fish, Early Life Stage Toxicity Test/Japanes medaka (*Oryzias latipes*)	Han et al. 2010 Filippin et al. 2007	NOEC	0.1	µg/L	Reliable with restrictions
Activated Sludge, Respiration Inhibition Test	No evidence of any adverse effects of ibuprofen on bacteria in any relevant test systems, as discussed in this ERA, with microbial biotransformation of ibuprofen having been shown to be significant.				

N/A=Not Analysed

Conclusions on studies:

Paracetamol is not a PBT substance. Considering the above data, paracetamol is not expected to pose a risk to the environment.

Ibuprofen is not a PBT substance. Considering the above data, ibuprofen is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics

Summary of paracetamol and ibuprofen pharmacokinetics
The pharmacokinetics of paracetamol and ibuprofen is well-known. Main pharmacokinetic characteristics obtained with the mono-components are summarised below. As this product is administered intravenously, the whole dose will be delivered directly into the systemic circulation and the bioavailability will be 100%.

Paracetamol
Absorption
Paracetamol is absorbed well when administered orally. Peak plasma concentration of paracetamol is achieved within ½-1 hour after oral administration. When administered as an iv infusion, the peak plasma concentration will be at the time when the infusion is stopped.

Distribution
Paracetamol is distributed rapidly into all tissues. Protein binding is low with recommended doses. The plasma half-life is approx. 2 hours.

Metabolism and excretion
Paracetamol is primarily metabolised in the liver by conjugation to glucuronide and sulphate. A small amount (about 3-10% of a therapeutic dose) is metabolised by oxidation by cytochrome P450 and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cysteine and mercapturic acid conjugates. Excretion occurs via the kidneys. Approx. 2-3% of a therapeutic dose is excreted unchanged, approx. 80-90% as glucuronide and sulphate and a smaller amount as cysteine and mercapturic acid derivatives.

Ibuprofen
Absorption
Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90% when administered orally. Peak serum concentrations occur one to two hours after oral administration. When

administered as an iv infusion, the peak plasma concentration will be at the time when the infusion is stopped, and the bioavailability will be 100%.

Distribution
Ibuprofen is extensively bound to plasma proteins (99%). Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.

Metabolism
Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates.

Excretion
Very little ibuprofen is excreted unchanged in the urine. The elimination half-life is approximately 2 hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

Pharmacokinetic studies
The pharmacokinetic documentation comprises two studies with Comboval.

Pharmacokinetic study (AFT-MXIV-01)
A Phase 1 Single-centre, single-dose, open-label, randomised, five-way crossover study to evaluate the pharmacokinetic parameters of Maxigesic® IV (intravenous paracetamol + intravenous ibuprofen), intravenous paracetamol, intravenous ibuprofen and Maxigesic® tablets, in healthy volunteers.

Compared to the oral combination tablet (Maxigesic), the iv combination product (Maxigesic IV) resulted in similar extent of exposure (AUC), but an about 2-fold higher C_{max}, both for paracetamol and ibuprofen. This is expected since the iv formulation deliver the whole dose directly into the systemic circulation during the 15-minute infusion time, whereas for the oral tablet formulation the C_{max} will be lower and appear later (later T_{max}) due to the time taken for disintegration, dissolution and absorption. Also, the metabolism during the first pass will contribute to the lower C_{max} after oral administration.

Thus, although differences in C_{max}, the Maxigesic iv product is considered to be acceptable bridged to the oral tablet Maxigesic based on similar systemic exposure, and to the iv products containing the mono-components ibuprofen and paracetamol, respectively.

Pharmacokinetic study (AFT-MXIV-06)
A Phase 1 Single-centre, single-dose, open-label, randomised, four-way crossover study to evaluate and compare the pharmacokinetic parameters of Maxigesic IV (intravenous acetaminophen + intravenous ibuprofen), Ofirmev (intravenous acetaminophen), Caldolor (intravenous ibuprofen) and Maxigesic 325 tablets, in healthy volunteers.

Based on the submitted bioequivalence study, Maxigesic IV (acetaminophen 1000 mg + ibuprofen 300 mg/100 ml) is considered bioequivalent with Orifmev (intravenous acetaminophen 1000 mg/ 100 ml), Caldolor (intravenous ibuprofen 400 mg/4 ml) and Maxigesic 325 tablets (acetaminophen 325 mg + ibuprofen 97.5 mg, BE based on AUC, not C_{max}, for the oral tablet).

Overall conclusions on pharmacokinetics:

Comboval, 10 mg/ml + 3 mg/ml, solution for infusion have the same dosing recommendation as other already approved products for iv administration of the mono-components paracetamol and ibuprofen in Europe and will therefore generate the same C_{max} and AUC. There are also approved iv combination product with paracetamol and ibuprofen in Europe.

Comboval, 10 mg/ml + 3 mg/ml, solution for infusion is acceptably bridged to the corresponding mono-components (paracetamol and ibuprofen) and FDC Maxigesic iv for iv administration. It is also bridged to Maxigesic oral FDC tablet (paracetamol and ibuprofen), based on similar total systemic exposure (AUC), not to C_{max}. However, the higher C_{max} (about 2-fold) for the iv infusion, compared to the oral tablets is judged not to be critical for the overall PK bridge as both C_{max} and AUC are bridged to the iv mono-components of paracetamol and ibuprofen, respectively.

Half the iv dose resulted in half the exposure showing that the pharmacokinetics is linear in this dose range.

There are no significant PK interactions between ibuprofen and paracetamol when given together as an iv infusion in this dose range.

The pharmacokinetics of paracetamol and ibuprofen is well-known.

Pharmacodynamics

Although the exact site and mechanism of analgesic action of paracetamol is not clearly defined, it appears that it induces analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P. It is used for the relief of mild to moderate pain and against fever. The primary mechanism of action might be the central inhibition of the prostaglandin synthesis, but its mechanism of action remains unclear and is the subject of continuing research. Paracetamol produces peripheral vasodilation yielding increased blood flow through the skin, perspiration and heat loss.

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase, leading to reduction in prostaglandin synthesis.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

The pharmacodynamics of paracetamol and ibuprofen are well-known.

Clinical efficacy

Two similar oral fixed-dose combination tablets of paracetamol/ibuprofen 500mg/150mg film-coated tablets (Maxigesic®, Combogesic®) have been developed for the adult population by AFT Pharmaceuticals Ltd.

On 18 May 2017, the European Medicines Agency completed an arbitration procedure following a disagreement among Member States of the European Union (EU) regarding the authorisation of the medicine Paracetamol/ibuprofen 500mg/150mg film-coated tablets. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Paracetamol/ibuprofen 500mg/150mg film-coated tablets outweigh its risks, and the marketing authorisation can be granted

in the United Kingdom and in the following Member States of the EU: Austria, Belgium, Croatia, France, Germany, Ireland, Luxembourg, the Netherlands, Portugal and Spain (referral, EMEA/H/A-29/001447).

With regard to oral administration, three clinical studies (AFT-MX-1, AFT-MX6 and AFT-MX-6E) in adults have compared efficacy and safety of the fixed-dose combination tablets (Maxigesic® and Combogesic®) with the active components used on their own and placebo and AFT-MX-3 explored the potency and safety of three different doses of the combination tablet compared to placebo.

The intravenous infusion product, which is the subject of this submission, was developed for the adult population and contains the same 3.3:1 ratio of paracetamol to ibuprofen as the existing tablets. It has been developed to extend the therapeutic use of oral Maxigesic® tablets to patients when administration by intravenous route is clinically justified by an urgent need to treat pain and/or when other routes of administration are not possible.

The applicant has conducted one pivotal phase III multiple-dose study of Maxigesic® IV (AFT-MXIV-07) to investigate the intravenous formulation in postoperative (bunionectomy) pain. The study investigated the effect and safety of Maxigesic® IV over comparable doses of iv paracetamol, iv ibuprofen and iv placebo.

Pivotal Efficacy Study (AFT-MXIV-07)

AFT-MXIV-07, the pivotal study of Maxigesic® IV, was a phase 3, placebo-controlled, prospective, randomised, double-blind, parallel-design trial comparing the analgesic efficacy and safety of Maxigesic® IV with paracetamol alone, ibuprofen alone and placebo, after bunionectomy surgery.

The main Inclusion Criteria for this trial were as follows:
 Male or female ≥ 18 and ≤ 65 years of age
 Classified as P1 to P2 in the American Society of Anaesthesiologists (ASA) Physical Status Classification System
 Has undergone distal, primary, unilateral, first metatarsal bunionectomy (with osteotomy and internal fixation) with no additional collateral bony procedures
 Experiences a pain intensity rating of ≥ 40 mm on a 100-mm Visual Analogue Scale (VAS) during the 9-hour qualification period after discontinuation of the post-surgical anesthetic block.
In total, 276 participants were randomised into the study.

Eligible participants were randomized in a 3:3:3:2 ratio to the following treatment groups:
 Maxigesic® IV (paracetamol 10 mg/mL + ibuprofen 3 mg/mL, 100 mL intravenous solution)
 Ibuprofen (ibuprofen 3 mg/mL, 100 mL intravenous solution)
 Paracetamol (paracetamol 10 mg/mL, 100 mL intravenous solution)
 Placebo 100 mL intravenous solution

Postoperatively, patients rated their pain intensity and pain relief at scheduled times throughout the 48 hours double-blind treatment period, including:
 Baseline (pain intensity only)
 5, 10, 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 5 hours after the first dose of the study drug
 Immediately before and 2 hours after each subsequent dose (doses 2-8) of the study drug while awake
 At the end of 48 hours of double-blind treatment period
 Immediately prior to the consumption of rescue medication

Study drug was administered by injection into a dedicated venous cannula, infused over 15 minutes every 6 hours (q6h regimen) for 48 hours after the first dose, with a maximum of 8 doses.
Subjects were allowed to receive supplemental rescue medication with an opioid product (oxycodone 5 or 10 mg every 4-6 hours as needed) after surgery and before randomization to help control breakthrough

pain if the regional anesthetic infusion fails to provide adequate anesthesia

The Intent-To-Treat (ITT) population, which consists of all subjects who receive at least 1 dose of study drug, was the primary population for the efficacy analysis.
For the primary efficacy endpoint, the time-adjusted Sum of Pain Intensity Differences over 48 hours (SPID48), was calculated from pain intensity scores recorded prior to the first dose of rescue.
Efficacy was also assessed in a series of secondary endpoints, including the Total Pain Relief (TOTPAR) and time-adjusted SPID scores over various time intervals (6, 12, 24 and 48 hours); VAS, Pain Intensity Difference (PID) and Pain Relief scores at each scheduled time point; as well as various time to event and rescue-based endpoints. The reporting of Treatment-Emergent Adverse Events (TEAEs) and changes in vital signs were used in the assessment of safety. Efficacy and Safety were assessed on the Intention To Treat and Safety populations, respectively. As there were no errors in the allocation of treatments, the two populations are identical.

Efficacy - primary endpoint

The mean time-adjusted SPID48 for each treatment group is presented in Table 11 and Figure 5. Maxigesic® IV provided significantly more pain relief than ibuprofen, paracetamol or placebo. The combination provided more than double the pain relief associated with either monocomponents (23.41 mm vs. 9.51 mm [ibuprofen] or 10.42 mm [paracetamol]).

Table 11: Summary of Time-adjusted SPID (0-48 hours) by Treatment Group (primary endpoint)
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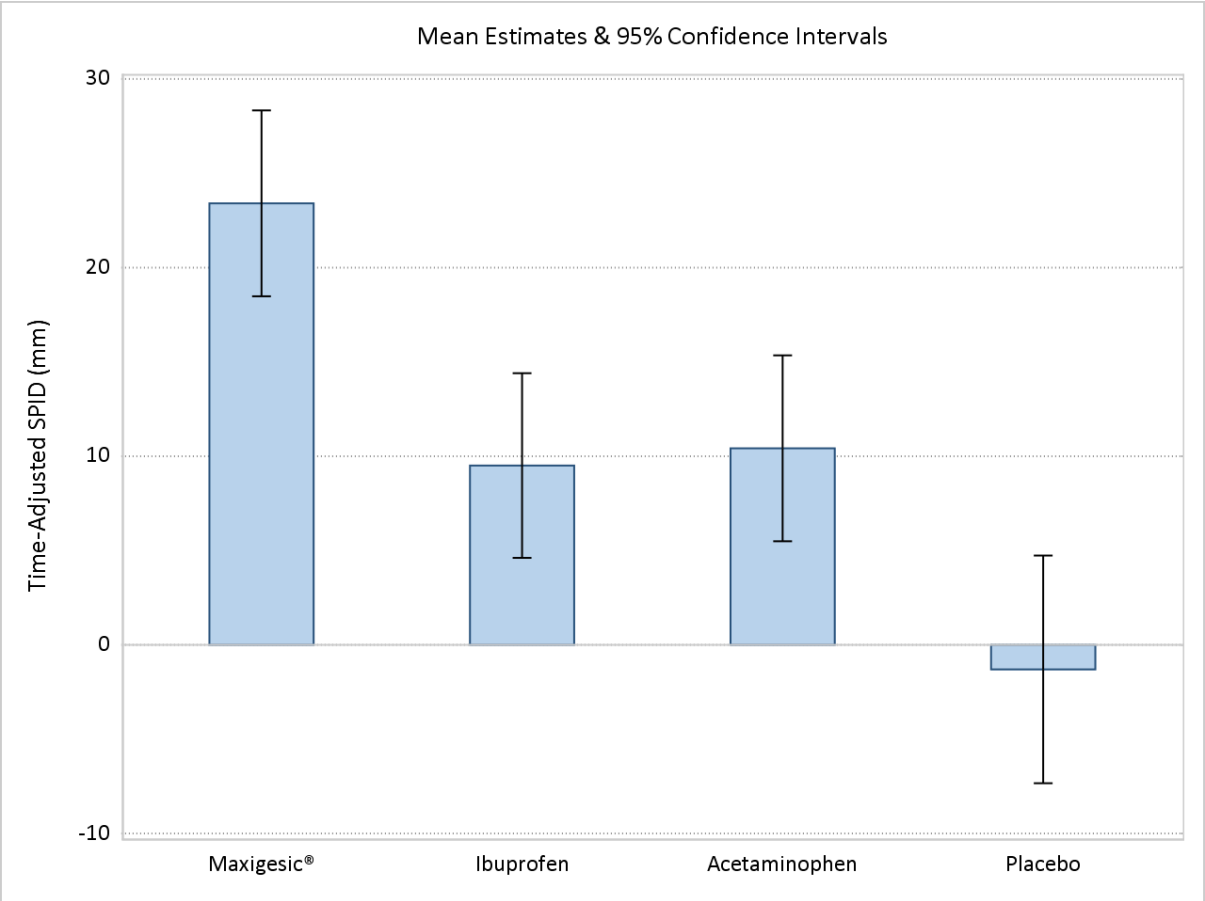
	Maxigesic IV	**Ibuprofen**	**Paracetamol**	**Placebo**
	N=75	**N=76**	**N=75**	**N=50**
N	75	76	75	50
Mean (SE)	23.41 (2.89)	9.51 (2.53)	10.42 (2.49)	-1.30 (2.08)
Median	23.10	5.40	3.45	-4.00
Min ; Max	-34.08 ; 74.17	-30.68 ; 79.98	-26.78 ; 65.43	-22.42 ; 47.50
Mean Estimate (SE)	23.41 (2.50)	9.51 (2.49)	10.42 (2.50)	-1.30 (3.07)
95% Confidence Interval	18.48 ; 28.34	4.61 ; 14.40	5.49 ; 15.35	-7.33 ; 4.74
Difference Estimate (SE)	-	13.90 (3.53)	12.99 (3.54)	24.71 (3.96)
95% Confidence Interval	-	6.95 ; 20.85	6.02 ; 19.96	16.92 ; 32.50
p-value	-	<0.001	<0.001	<0.001

Figure 5: Time-adjusted SPID$_{48}$ up to first dose of rescue medication.



Three Sensitivity Analyses were conducted to assess the robustness of the derivation of the primary endpoint. In each case the time-adjusted SPID48 was derived slightly differently, as outlined below:

1. Time-adjusted SPID48 calculated with the first pre-rescue VAS score carried forward to the end of participation in the study (first rescue observation carried forward [ROCF] to end)
2. Time-adjusted SPID48 derived from all VAS scores (scheduled and Pre-rescue)
3. Time-adjusted SPID48 derived from all VAS scores with each pre-rescue VAS carried forward up to 4 hours (ROCF 4 hours)

Overall, the results of the sensitivity analyses confirm that of the primary analysis and demonstrate the robustness of the endpoint. In each case the combination was significantly superior to ibuprofen and paracetamol monotherapy groups (all $p<0.01$).

In summary, the results of the pivotal IV study with paracetamol 10 mg/mL + ibuprofen 3 mg/mL showed that the Sum of Pain Intensity Differences over 48 hours (SPID48), which was the primary efficacy endpoint, was significantly higher for the iv-combination treatment compared to the monotherapies and placebo and that Maxigesic® IV provided significantly better pain relief.

Efficacy - secondary endpoints

The mean VAS pain intensity and Pain Intensity Difference (PID) scores from scheduled time points during the entire 48-hour study period, respectively. VAS and PID scores at each time point were

anlysed by ANCOVA (with baseline pain as covariate). Pairwise comparisons on the mean VAS scores and mean PID scores revealed that:

 Maxigesic® IV provided significantly greater pain relief than placebo at each time point between 10 minutes and 48 hours (6 hours after 8th dose) after the first dose
 Maxigesic® IV provided significantly greater pain relief than paracetamol at each time point between 5 minutes and 48 hours after the first dose
 Maxigesic® IV provided significantly greater pain relief than ibuprofen at each time point between 45 minutes and 48 hours after the first dose, with the exception of the score at 26 hours (2 hours after the fifth dose)

The other secondary endpoints of this study support the primary endpoint in demonstrating the superiority of the combination with respect to comparable doses of each ingredient used alone. These results are summarized below:

• Significantly greater pain relief over 6, 12, 24 and 48 hours (time-adjusted SPIDs and TOTPARs) and study participation (Global Pain Rating)
• Significantly lower odds of requiring opioid rescue
• Significantly longer time to first use of rescue medication
• Significantly lower consumption of opioid rescue over 24 and 48 hours
• Significantly greater Peak Pain relief obtained over a longer time interval
• The shortest Time to Perceptible Pain Relief, which was significant versus paracetamol and placebo
• The shortest Time to Meaningful Pain Relief, which was significant versus ibuprofen and placebo
• The highest response rate, which was significant versus ibuprofen and placebo
• The shortest time to response, which was significant versus paracetamol and placebo

Maxigesic® IV provided significantly greater pain relief (measured by the mean VAS pain intensity and Pain Intensity Difference (PID) scores) than placebo, ibuprofen and paracetamol at nearly all time points during the 48 hours. Overall, the results on the secondary endpoints in the pivotal study are supportive of efficacy of Maxigesic® IV on SPID48 (primary endpoint).

Use of rescue medication
Whereas patients in the Maxigesic® IV Combination group experienced a longer time to the first dose of rescue medication, and a lower consumption of oxycodone rescue over the first 24 hours and the entire 48 hours study period than all three comparator groups ($p<0.05$), the use of rescue medication (opioids) was, overall, rather high (75%, 92%, 93% and 96% of patients require rescue medication at least once for combination treatment, ibuprofen, paracetamol and placebo, respectively) and the time until the first rescue usage was short (median time to rescue is 3.32h, 1.68h, 1.08h and 1.18h for combination treatment, ibuprofen, paracetamol and placebo, respectively). The use of rescue medication may be related to a quite high baseline pain level (mean VAS score was 66 to 69 mm prior to treatment) in the IIT population of this study.

Supportive studies in adults using oral 500 mg paracetamol and 150 mg ibuprofen formulation

The applicant provides an overview of four AFT-sponsored supportive studies that evaluated the efficacy of the oral FDC tablet formulations, Maxigesic® and Combogesic® in adults, AFT-MX1, AFT-MX 6, AFT-MX6E and AFT-MX3. These studies have been evaluated and discussed in a previous procedure by the CHMP (referral EMEA/H/A-29/001447). The CHMP concluded that the

oral fixed-dose combination of 500 mg paracetamol and 150 mg ibuprofen is safe and effective in acute to moderate pain in adults, including the elderly. The oral FDC combination was more effective than the individual components, while its safety profile was similar. Given that pharmacokinetic data (studies AFT-MXIV-01 and AFT-MXIV-06) showed that the intravenous and oral forms of the FDC paracetamol and ibuprofen product are bioequivalent in terms of AUC (see discussion in the pharmacokinetics section), the efficacy data of the oral FDC tablet are regarded as supportive to the efficacy of the IV FDC.

Conclusion on clinical efficacy

In the pivotal clinical efficacy study (AFT-MXIV-07), using the Bunionectomy surgical pain model, intravenous administration of the fixed dose combination with paracetamol 10 mg/ml and ibuprofen 3 mg/ml per 100 ml, IV, indicates a significantly better analgesic efficacy of the IV combination product with statistical superiority over the IV mono-components and IV placebo.

In a previous procedure for the oral fixed dose combination of Paracetamol/ Ibuprofen 500mg/150mg film coated tablets, the CHMP considered the benefit-risk balance as adequately demonstrated for the oral combination for the indication acute to moderate pain in adults, including the Elderly and for the use up to three days as result of the referral procedure under Article 29(4) of Directive 2001/83/EC (EMEA/H/A-29(4)/1447, Doc. Ref EMA/517503/2017). Moreover, since the pharmacokinetic data indicate that the intravenous and oral forms of the FDC product are bioequivalent in terms of AUC (see discussion in the pharmacokinetics AR), the bridging of efficacy of the IV FDC to the FDC tablet is regarded as possible. Consequently, the efficacy data generated with the FDC tablet are considered supportive for the claim of efficacy of the IV FDC.

In addition, the combination therapy appears to have a rescue medication sparing effect and mostly provides better pain relief on the secondary endpoints tested.

The proposed treatment of acute moderate pain up to a maximum of two days with the fixed dose combination with paracetamol 10 mg/ml and ibuprofen 3 mg/ml per 100 ml, IV, is considered to have been sufficiently justified taking into account the efficacy data presented in the pivotal study undertaken with the FDC IV formulation in conjunction with the supportive studies conducted with the FDC tablet form and the available literature.

In conclusion, efficacy of the IV combination with paracetamol 10 mg/mL and ibuprofen 3 mg/mL for the short duration of use of 2 days for the symptomatic treatment of moderate pain has been satisfactorily demonstrated.

Clinical safety

Pivotal Efficacy Study (AFT-MXIV-07)
Safety data obtained from the phase 3 clinical study of Maxigesic® IV in the treatment of acute postoperative pain following bunionectomy surgery.

No Serious Adverse Events (SAEs) were reported in this study and 3 patients discontinued from the study due to adverse events (pyrexia [paracetamol group], allergic reaction/angioedema and burning sensation at IV site [ibuprofen group]).

An overview of AEs in AFT-MXIV-07 is provided in Table 1. In total, 493 adverse events were experienced by 194 (70.3%) of the 276 patients in this study. 3% of adverse events in this study were severe (15/493), 5% of patients experienced an AE rated as severe, with the paracetamol group having the highest incidence (8.0%). 18% of adverse events were deemed definitely or probably related to the

study medication (90/493), 20% of patients experienced an AE deemed definitely or probably related to the study medication, and the incidence was comparable in the Maxigesic® IV, ibuprofen and placebo groups (20-28%) and lowest in the paracetamol group (11%) (Table 1).

Table 1: Summary of Adverse events from AFT-MXIV-07.

	Maxigesic IV	*Ibuprofen*	*Paracetamol*	*Placebo*	*Total*
	N=75	*N=76*	*N=75*	*N=50*	*N=276*
Patients reporting AEs, N (%)	52 (69.3%)	58 (76.3%)	45 (60%)	39 (78%)	194 (70.3%)
AEs Reported, n	142	131	112	108	493
AEs per subject, n/N	1.89	1.72	1.49	2.16	1.79
Patients with severe AEs, N (%)	3 (4%)	4 (5%)	6 (8%)	1 (2%)	14 (5%)
Patients with AEs Definitely/Probably related, N (%)	17 (23%)	15 (20%)	8 (11%)	14 (28%)	54 (20%)

Common AEs are AEs that were reported in more than 10% of the 276 participants randomized to treatment in this study. AEs coded to Gastrointestinal Disorders or Nervous System Disorders accounted for 60% of AEs (GI: 190, NS: 107, Total: 493). This is consistent with the postoperative setting and what has been observed in previous postoperative pain studies with the Maxigesic® oral formulation (Table 2).

Table 2: Common[1] Treatment-Emergent Adverse Events – Safety Population

System Organ Class Preferred Term	Maxigesic® N=75		Ibuprofen N=76		Acetaminophen N=75		Placebo N=50		Total N=276	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events
Any Class, Any Term p-value[2]	52 (69.3%)	142	58 (76.3%) 0.365	131	45 (60.0%) 0.305	112	39 (78.0%) 0.312	108	194 (70.3%)	493
Gastrointestinal disorders p-value[2]	29 (38.7%)	66	32 (42.1%) 0.741	49	28 (37.3%) 1.000	47	18 (36.0%) 0.851	28	107 (38.8%)	190
Nausea p-value[2]	22 (29.3%)	37	26 (34.2%) 0.601	33	25 (33.3%) 0.725	28	16 (32.0%) 0.843	22	89 (32.2%)	120
Vomiting p-value[2]	16 (21.3%)	24	5 (6.6%) 0.010	8	11 (14.7%) 0.396	12	1 (2.0%) 0.001	1	33 (12.0%)	45
Nervous system disorders p-value[2]	23 (30.7%)	32	17 (22.4%) 0.273	21	20 (26.7%) 0.718	24	19 (38.0%) 0.442	30	79 (28.6%)	107
Dizziness p-value[2]	13 (17.3%)	18	7 (9.2%) 0.157	8	7 (9.3%) 0.229	8	8 (16.0%) 1.000	10	35 (12.7%)	44
General disorders and administration site conditions p-value[2]	15 (20.0%)	22	17 (22.4%) 0.843	18	8 (10.7%) 0.173	9	13 (26.0%) 0.513	15	53 (19.2%)	64
Skin and subcutaneous tissue disorders p-value[2]	11 (14.7%)	15	15 (19.7%) 0.519	17	10 (13.3%) 1.000	11	7 (14.0%) 1.000	14	43 (15.6%)	57

[1] Incidence > 10% in Total group
[2] Fisher's two-sided exact test with Maxigesic®

According to pairwise comparisons of the incidence of common AEs, the incidence of vomiting was significantly higher in the Maxigesic® IV group compared with the ibuprofen and placebo groups, but not the paracetamol group, suggesting that the vomiting reported by patients in the Maxigesic® IV group is attributable to the paracetamol component of the combination, rather than a unique effect. There were no other differences in the incidence of common AEs between the Maxigesic® IV group

and the other groups.

In general, the observations on the safety of Maxigesic® IV in this pivotal study are consistent with what has been observed in previous analgesic studies conducted with the oral solid formulation (acetaminophen 500 mg + ibuprofen 150 mg/tablet) (AFT-MX-1, AFT-MX-3 and AFT-MX-6E). Gastrointestinal disorders were most common, being reported by 38.8% of all patients and accounting for 38.5% of all treatment-emergent events. The CHMP has previously concluded that the benefit-risk balance as adequately demonstrated for Paracetamol/ Ibuprofen 500mg/150mg film coated tablets for the indication mild to moderate pain in adults, including the Elderly and for use up to three days as result of the referral procedure under Article 29(4) of Directive 2001/83/EC (EMEA/H/A-29(4)/1447, Doc. Ref EMA/517503/2017). The risks of adverse events have been further limited by restricting the treatment duration to maximum 2 days in the intended indication, since the treatment period of the IV FDC in the pivotal clinical study was conducted over 2 days.

Supportive Studies with Maxigesic® and Combogesic® tablets

AFT-MX-1
Safety data obtained from a phase 3 study (postoperative dental pain model) of Maxigesic® tablets

AFT-MX-6E
Safety data obtained from a phase 3 study (arthroscopic pain model) of Maxigesic® tablets

AFT-MX-6
Safety data obtained from one phase 3 study (postoperative dental pain model) of Combogesic® tablets

AFT-MX-3

Safety data obtained from a phase 2 dose-response study of Maxigesic® tablets

Summary of Safety from Clinical Efficacy Literature

The Applicant presents a Summary of Safety from Clinical Efficacy Literature which looks at safety outcomes after intravenous treatment with paracetamol and ibuprofen, iv paracetamol and other NSAIDs, iv paracetamol single therapy and iv ibuprofen single therapy in the treatment of postoperative pain. Furthermore, a Summary of Safety from other pain models is presented.

This looks at safety outcomes of iv treatment with paracetamol and other NSAIDs. It also reviews safety outcomes of single iv paracetamol treatment looking at studies

A) Reporting no adverse events, B) Studies comparing paracetamol to placebo, C) Studies comparing paracetamol to other treatments, D) Summary of incidence of adverse effects related to paracetamol.

Lastly it also reviews safety outcomes of iv ibuprofen as single treatment in other pain models.

Overall, the safety data from the supportive studies undertaken with tablets in adults and the Summary of Safety from Clinical Efficacy Literature presented by the Applicant does not indicate a significantly different safety profile of the iv combination therapy compared to the iv single therapies. The FDC is regarded as well tolerated in the short-term treatment in adults as well as in Elderly population. of this subgroup.

Post marketing experience

This proposed fixed dose intravenous combination product Maxigesic® IV has been developed as a direct line extension of Maxigesic® tablets (paracetamol 500 mg/ibuprofen 150 mg).

The oral formulation (Maxigesic®) has been available in New Zealand, the country of origin, since 2009, and in Australia since 2013. It has now been approved in 32 countries worldwide. Between October 2009 and April 2018 more than 162 million tablets were sold in the worldwide.

Since the product was launched, 6 adverse drug reaction (ADR) reports from New Zealand and Australia have been received by the sponsor, including 1 serious ADR and 5 non-serious ADRs. From the European market (Italy), 5 adverse drug reaction (ADR) reports have been received by the sponsor, 4 of which were serious. In total, 11 ADRs have been reported to the sponsor, including 5 serious ADRs, thus confirming the safe and well-tolerated profile of this product.

Summary of clinical safety

The clinical trials sponsored by AFT Pharmaceuticals have demonstrated that intravenous and oral forms of Maxigesic® and Combogesic® are well tolerated and have a comparable incidence of adverse events versus monocomponents and placebo and no unique safety signal was observed in patients treated with the combination.

From the clinical literature, intravenous paracetamol and ibuprofen have been shown to be well tolerated. The systematic literature review only identified one study which administered both intravenous paracetamol and intravenous ibuprofen (1000 mg and 800 mg, respectively) (Gupta et al., 2016). In this study, the patients treated with both drugs had a reduced incidence of adverse events compared to ibuprofen alone. Collectively, the studies which combined intravenous paracetamol with another NSAID showed that the incidence of adverse events was either unchanged or reduced in patients treated with paracetamol/NSAID in comparison to the individual components. A vast number of studies have administered intravenous paracetamol, and this has been found to be well tolerated. A comparatively fewer number of studies have examined the safety of intravenous ibuprofen, nevertheless, these have all shown that intravenous ibuprofen is well tolerated.

An integrated safety analysis for intravenous ibuprofen was published in 2015 (Southworth et al., 2015) that covered five sponsored studies covered by the present review (Kroll et al., 2011; Krudsood et al., 2010; Promes et al., 2011; Singla et al., 2010; Southworth et al., 2009), in addition to three studies that were not included, and two unpublished studies. This analysis covered 1,220 patients treated with intravenous ibuprofen, and 452 patients who received placebo and 80 patients who received ketorolac as a comparator. Most of the patients received intravenous ibuprofen for surgical pain (n = 987). In studies where all adverse events were collected, 1149 patients received at least one dose of ibuprofen, 60% of whom experienced at least one adverse event, most of which were of mild (53%) or moderate (38%) severity. The incidence of adverse events was higher in placebo-treated patients (85%), with these being mild (56%), moderate (38%) or severe (6%). The most common adverse events in all groups were nausea (26% in ibuprofen, 47% in placebo), vomiting (9% in ibuprofen, 14% in placebo), constipation (7% in ibuprofen, 14% in placebo) and flatulence (7% in ibuprofen, 10% in placebo). The only adverse event that was more frequent with ibuprofen

administration was infusion site pain. Across the ten clinical studies, 5% of ibuprofen-treated and 4% of placebo-treated patients experienced a serious adverse event. A total of eleven deaths occurred, 0.6% in each treatment group, none of which were deemed to be related to the study medication. The analysis reported that overall, intravenous ibuprofen is well tolerated, and results in fewer adverse events than placebo with morphine rescue.

Collectively, the clinical literature supports the studies sponsored by AFT Pharmaceuticals Ltd., that show that combined treatment with paracetamol and ibuprofen, either as an intravenous or oral formulation, is well tolerated.

Conclusion on clinical safety

The safety profiles of paracetamol and ibuprofen as single substances are well known.

The main concern for the IV combination therapy is a potential unnecessary exposure to both substances when one might be enough to achieve the desired effect and possible additive side effects on the GI tract, liver, cardiovascular system and renal function. The treatment with the IV combination should therefore be reserved for clinical scenarios where treatment with the IV mono-components is not likely to deliver the desired pain-relieving effect against moderate pain and where an intravenous route of administration is considered clinically necessary and/or when other routes of administration are not possible.

The AEs per subject were approximately 2-3 times higher in all arms of the pivotal study compared to the AEs per subject in the supportive studies. However, because AEs per subject were higher in all arms of the pivotal study and highest in the IV placebo arm the increase appears to be related to the application form rather than the combination treatment. It should be a noted that, in general, IV treatment is associated with higher rates of AEs compared to oral administration.

The presented safety data from the pivotal effect and safety study AFT-MXIV-07 does not indicate a significantly different safety profile of the IV-combination therapy compared to the IV single therapies. However, as the treatment period was conducted over two days in the study AFT-MXIV-07, the maximum treatment time of the IV FDC has also been limited to two days in the intended indication, as outlined in the SmPC document.

The provided study AFT.MXIV-07 or the supportive studies did not include safety data of the intravenous combination therapy in the Elderly population. However, the safety profile for the treatment of the Elderly with the FDC tablets up to three days is acceptable also shown in the positive B/R assessment by the CHMP where safety in the Elderly population has been specifically assessed. Limiting the maximum time of treatment to two days allows for safe handling of this product in general and specifically in the Elderly.

In conclusion, based on review of the clinical safety and efficacy data, the benefit/risk balance of Comboval is considered positive, and the application can therefore be recommended for approval from a clinical standpoint.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Comboval (Paracetamol/Ibuprofen IV, 10 mg/ml + 3 mg/ml, solution for infusion).

Safety specification

Summary table of safety concerns in RMP version 1.0 as proposed by the applicant:

Summary of safety concerns for ibuprofen

Important identified risks	None
Important potential risks	None
Missing information	None

Summary of safety concerns for paracetamol

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data and the Applicant’s response to the questions raised by RMS and

CMSs on quality, safety and efficacy, the present application for Comboval is considered approvable.

Since there are no outstanding issues, the overall benefit/risk balance is considered positive the application is recommended for approval.

The SmPC is considered acceptable.

There is no need for conditions under Article 21a/22 of Directive 2001/83.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Comboval, 10 mg/ml +3 mg/ml, Solution for infusion, was positively finalised on 2021-05-26.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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