LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Paracetamol/Ibuprofen Vale

(paracetamol/ibuprofen)

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This module reflects the scientific discussion for the approval of Paracetamol/Ibuprofen Vale. The procedure was finalised on 2020-04-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Vale Pharmaceuticals Limited has applied for a marketing authorisation for Paracetamol/Ibuprofen Vale, 10 mg/ml + 3 mg/ml, solution for infusion. The active substances are paracetamol (analgesic by elevation of the pain threshold) and ibuprofen (analgesic, anti-inflammatory and anti-pyretic).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

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

III.1 Introduction

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.

III.2 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.

III.3 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.

III.4 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.

III.5 Ecotoxicity/environmental risk assessment

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}	134	mg/L	*Scenedesmus subspicatus*

	Environment Canada standard method	IC_{25}	32	µg/L	*Selanastrum capricornutu*
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	

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	NOEC	10	µg/L	*Selanastrum capricornutum*
	Cleuvers, 2006	NOEC	32	mg/L	*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.				

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.

III.6 Discussion on the non-clinical aspects

There are no non-clinical issues identified precluding a marketing authorisation and Paracetamol/Ibuprofen Vale, 10 mg/ml + 3 mg/ml, solution for infusion, is recommended for approval.

IV. CLINICAL ASPECTS

IV.1 Introduction

Two similar fixed-dose combination tablets have been developed for the adult population by AFT Pharmaceuticals Ltd. These products are approved under the trade names Maxigesic® (paracetamol 500 mg + ibuprofen 150 mg) in New Zealand, Australia, UAE, Singapore, Malaysia (marketed in Australia and New Zealand) and under various other tradenames in more than 25 European countries (marketed in more than 15 European countries), and Combogesic® (paracetamol 325 mg + ibuprofen 97.5 mg, also referred to as Maxigesic® 325), which is pending registration in the USA and Canada. In 2017, the EMA Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Paracetamol/ibuprofen 500mg/150mg film-coated tablets (Maxigesic, Combogesic) outweigh its risks for the treatment of mild to moderate pain in adults up to max three days, and the marketing authorisation could 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).
The intravenous infusion product, which was 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 advantage of 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.
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.
Additionally, a pivotal phase III multiple-dose study of Maxigesic® IV (AFT-MXIV-07) was conducted to investigate the intravenous formulation in post bunionectomy-operation pain. The study investigated the effect and safety of Maxigesic® IV over comparable doses of iv paracetamol, iv ibuprofen and iv placebo.

IV.2 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 intravenous paracetamol/ibuprofen.

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 (acetaminophen 1000 mg/ 100 ml), Caldolor (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).

Results for the individual components after iv dosing published in scientific literature are comparable to those found for paracetamol and ibuprofen in the PK studies conducted by the Applicant.

Overall conclusions on pharmacokinetics
The pharmacokinetics of paracetamol and ibuprofen is well-known.

Paracetamol/Ibuprofen Vale, 10 mg/ml + 3 mg/ml, solution for infusion has 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.

Paracetamol/Ibuprofen Vale, 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.

The suggested infusion time of 15 minutes will result in C_{max}-values similar (paracetamol) or lower (ibuprofen), compared to approved mono-component products for iv infusion of paracetamol and ibuprofen. The C_{max} values for paracetamol and ibuprofen are therefore not considered to be a safety issue.

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.

IV.3 Pharmacodynamics

The pharmacodynamics of paracetamol and ibuprofen are well-known.

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.

IV.4 Clinical efficacy

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.

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

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 primary efficacy endpoint Sum of Pain Intensity Differences over 48 hours (SPID48) was found to be significantly higher for the iv combination treatment compared to the monotherapies and placebo i.e. Maxigesic® IV provided significantly better pain relief. Maxigesic® IV also 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 study period. However, Maxigesic® IV did not provide significantly greater pain relief measured as mean pain relief over time compared to paracetamol at five scheduled time points and compared to ibuprofen at four time points(but at all other time points). Although not significantly, the pain intensity differences were higher for Maxigesic® nevertheless.

The other secondary endpoints showed that the combination provided
 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 but not ibuprofen.
 The shortest Time to Meaningful Pain Relief, which was significant versus ibuprofen and placebo but not paracetamol.
 The highest response rate, which was significant versus ibuprofen and placebo but not paracetamol. However, the response rate of 51% for Maxigesic compared to 34% for ibuprofen and 36% for paracetamol was less than expected
 The shortest time to response, which was significant versus paracetamol and placebo but not ibuprofen.
Significantly fewer patients in the Maxigesic® group (75%) required rescue medication (oxycodone or morphine) compared with 92% of patients in the ibuprofen group, 93% of patients in the paracetamol group and 96% in the placebo group.
Over the entire 48-hour, double blind treatment period, the median oral morphine milligram equivalent (MME) of all rescue medication consumed was lowest in the paracetamol/ibuprofen group (30 mg), and significantly lower than consumption in the ibuprofen (43.5 mg, p=0.008), paracetamol (45 mg, p=0.004) and placebo groups (67.5 mg, p<0.001).

In conclusion the pivotal study has shown that the combination treatment is superior over the mono components and placebo. However, some of the secondary endpoints indicate that the advantage is not as high as expected. Especially in the elderly a step by step approach with the single components may be more appropriate given the increased risks for GI, cardiovascular, renal and hepatic side effects. Alternatively, in some cases a reduced dose of the combination therapy could be considered.

Supportive studies in adults:
The applicant provided an overview of 4 AFT-sponsored supportive studies that evaluated the efficacy of the oral tablet formulations, Maxigesic® and Combogesic® in adults, AFT-MX1, AFT-MX 6, AFT-MX6E and AFT-MX3.

Acute Pain Model-Phase 3 Dental Pain Study(AFT-MX-1)
This study was a prospective, parallel group, double-blind comparison of the analgesic effect of a combination of paracetamol and ibuprofen (Maxigesic®), paracetamol alone, or ibuprofen alone in

patients with post-operative pain. Patients aged 16 years and older undergoing oral surgery, including the extraction of at least one lower third molar tooth under local or general anesthetic, were randomized into three groups, each to receive two tablets pre-operation and then 6 hourly up to 48 hours after the first dose.

Group A were randomized to two tablets per dose of paracetamol 500 mg, Group B to ibuprofen 150 mg and group C to Maxigesic®, which contains paracetamol 500 mg + ibuprofen 150 mg. The total dose of each drug in 24 hours were: Group A, paracetamol 4000 mg; Group B, ibuprofen 1200 mg; Group C, paracetamol 4000 mg + ibuprofen 1200 mg. Recruitment continued until 120 patients were available for the intent to treat population for the primary analysis.
Analgesia, the primary efficacy end point, was evaluated as the time-adjusted AUC calculated from 100 mm VAS pain scores over 48 hours at both rest and on activity. The VAS records were taken at one to two hour intervals while awake.

The primary end point assessed on the Intent to Treat (ITT) population, showed the mean time-adjusted AUCs over 48 hours calculated from the VAS pain scores for Maxigesic® were significantly lower than for paracetamol at rest (22.344 [SE 3.2] and 33.016 [SE 3.005] respectively (p=0.007), and on activity 28.377 [SE 3.396] and 40.364 [SE 3.271] respectively (p=0.006).
A similar outcome is seen for the Maxigesic® comparison where the AUCs over 48 hours showed the VAS for the combination drug were significantly lower than for ibuprofen at rest, 22.344 [SE 3.2] and 34.78 [SE 3.22] respectively (p=0.003) and during activity 28.377 [SE 3.396] and 40.217 [SE 3.418] respectively (p=0.007)

A presentation of the pain records during the 48 hours also shows the Maxigesic® analgesic effect has a faster onset than either of its two active ingredients and superior analgesia at almost all time points at both rest and during activity.
A Global Pain Rating scale where patients recorded their pain as nil, mild, moderate or severe, showed the Maxigesic® treated patients had a significantly lower pain rating (nil or mild) than paracetamol 68.4% vs 37.5%, p=0.008) and numerical but not significant lower rating than ibuprofen (68.4% vs 54.3%). For patients recording their pain as moderate or severe at the end of the observation period, the comparative values were Maxigesic® 31.6%, ibuprofen 45.7% and paracetamol 62.5%. These strongly statistically significant outcomes show unequivocally the analgesic superiority of Maxigesic® over each of paracetamol and ibuprofen administered at their maximum recommended daily doses.

The study concluded that Maxigesic® showed significantly superior analgesia compared to either of its two active ingredients alone, exhibiting this analgesic advantage throughout the 48 hour treatment period without significant added safety penalties. The results of this study were published in the British Journal of Anaesthesia (Merry et al., 2010).

Assessing this study, it can be said that there was no placebo arm which can be defendable from the ethical point of view. What the clinical overview did not mention is the relatively small number of study subjects of 40 per group. Nevertheless, the differences of the mean time-corrected AUC on rest and activity are statistically significant but clinical relevance can be debatable as the differences are relatively small (translated to around 9-10 mm in the VAS scale). Although this translates into a 30% reduction of modest levels of pain, a 50% reduction would be clinically “successful/important” according to Wilhelmus et al., Pain Research&Management from 2013, “What constitutes a clinically important pain reduction in patients after third molar surgery?”

AFT-MX-6 is another phase 3, placebo-controlled, prospective, randomised, double-blind, parallel-design trial with a safety follow up at Day 30. The clinical efficacy and safety of Combogesic® (paracetamol 325 mg + ibuprofen 97.5 mg per tablet, 3 tablets per dose, dosed every 6 hours for 48 hours) were compared to its individual components (either paracetamol 325 mg or ibuprofen 97.5 mg) and placebo after dental surgery. The primary efficacy objective of this trial was to compare the time adjusted Summed Pain Intensity Differences (SPIDs) derived from the VAS pain intensity scores up to 48 hours after the first dose of study medication among the four study groups. Data from 408

participants were available for ITT analysis of the time-adjusted SPID48 derived from the VAS pain intensity scores recorded during the 48 hour double-blind phase.
The analysis of time-adjusted SPID48 demonstrated that Combogesic® (mean=31.56, SE=1.94) provides more effective pain relief than placebo (mean=14.86, SE=2.26), paracetamol (mean=17.71, SE=1.89) or ibuprofen (23.18, SE=1.89) with a high level of statistical significance ($p<0.001$).
The average VAS pain intensity score in each study group over the 48 hours was plotted. Subjects in the Combogesic® group had the lowest average pain intensity level compared to the other three study groups, trend observed already during the first 6 hours, representing the first dosing interval.
Subjects in Combogesic® group had a similar onset of action than ibuprofen and paracetamol as "perceptible pain relief" but the subjects in the Combogesic® group had a significantly faster onset of meaningful pain relief.
Another secondary endpoint was the maximum pain intensity which was significantly lower for the Combogesic® group compared with the single substances and placebo.
The highest response rate who achieved at least 50% reduction in baseline pain prior to the first dose of rescue medication. was observed in the Combogesic® group (87.2%) and the lowest response rate occurred in the placebo group (37.3%) and there were fewer subjects in the ibuprofen (76.6%) or the paracetamol group (69.4%) than those in the Combogesic® group. The difference between the Combogesic® group and the other three treatment groups was statistically significant ($p\leq0.042$).
Median time to at least a 50% reduction in baseline VAS pain in these patients was the shortest in the Combogesic® group and the longest in the placebo group (0.75 and 7 hours respectively, $p<0.001$).
Median time to a 50% reduction in baseline pain in the Combogesic® group was faster for the combination than both monotherapy groups (0.75 hours vs. 1.5 hours for ibuprofen and 1.00 hour for paracetamol) and significance was obtained for the comparison with paracetamol ($p=0.025$)
Participants in the placebo group experienced the shortest time to the requirement of rescue medication (mean = 9.90 hours) and participants in the Combogesic® group experienced the longest time to the requirement of rescue medication (mean = 37.53 hours). As fewer than 50% of the subjects in the Combogesic® and ibuprofen group required rescue, the median time to require of rescue could not be estimated in these groups. The difference between the Combogesic® and the other three study groups was statistically significant ($p<0.014$).
Overall, 188 (46.3%) subjects took rescue medication out of 406 subjects. The proportion of subjects that required at least one dose of rescue medication was highest in the placebo group (81.3%) and lowest in the Combogesic® group (23.9%). In the active comparator groups over 40% of subjects required at least one dose of oxycodone. This suggested that subjects in Combogesic® group experienced lower pain intensity level as the study medication was more effective at controlling postoperative pain. The difference between the Combogesic® group and any one of the other three treatment groups (placebo, paracetamol or ibuprofen) was statistically significant ($p<0.001$ vs paracetamol or placebo, $p=0.002$ vs. ibuprofen).
The rescue medication consisted of oxycodone 5-10 mg (5 mg per tablet) every 4-6 hours as required. The mean amount of rescue consumed was greatest in the placebo group (17.9 mg), followed by the paracetamol (11 mg), ibuprofen (7.1 mg) and Combogesic® groups (3.7 mg). The difference in consumption between the Combogesic® group and the other 3 treatment groups reached statistical significance ($p<0.001$ vs paracetamol or placebo, $p=0.003$ vs. ibuprofen).
In the Combogesic® group, 63.5% subjects evaluated their study medication as "Very good" or "Excellent". The proportion of such ratings in the ibuprofen, paracetamol and placebo groups were 40.7%, 35.8% and 6.6% respectively. The pairwise comparisons of Combogesic® group and the other three treatment groups were statistically significant according to the Mann-Whitney U test ($p\leq0.003$).
Overall, the primary and secondary endpoints of this study support a conclusion that a fixed-dose combination of paracetamol 325 mg + ibuprofen 97.5 mg per tablet, with three tablets comprising a full dose (total paracetamol 975 mg + ibuprofen 292.5 mg) provides superior analgesia to comparable doses of either monotherapy alone or placebo.

In conclusion this study is probably the most convincing one within the presented supportive studies showing significantly better effect of the combination tablet over the single substances and placebo. It also showed mostly superiority in the second endpoints. However, the third molar pain model is not fully predictable for other pain conditions.

Another phase 3 study (AFT-MX-6E) evaluated the efficacy of Maxigesic® against placebo and its active mono-components. Post-operative knee arthroscopy pain was treated with Maxigesic® 4000mg/1200 mg per day, with paracetamol 4000 mg per day, ibuprofen 1200 mg per day or placebo. Maxigesic® was statistically better than placebo but not better than paracetamol or ibuprofen given as single therapy.

In conclusion paracetamol or ibuprofen were not significantly better compared to placebo, only the FDC tablet was. The FDC tablet was however not significantly better than the single therapies. Even if not shown in this study, an additional pain-relieving effect when combining paracetamol and ibuprofen compared to the effect of only one of the two components is expected in many cases. However, in the majority of cases of mild to moderate pain, treatment with paracetamol or ibuprofen alone is usually sufficient. Combining analgesics, especially in a fixed combination, is clinically a second line treatment when single drug therapy fails.

A dose ranging study (AFT-MX-3) compared the efficacy of Maxigesic® doses of 4000mg/1200 mg paracetamol/ibuprofen during 24 hours, Maxigesic® 2000 mg/600 mg during 24 hours, Maxigesic® 1000mg/150 mg during 24 hours to placebo. The study was conducted in patients following third molar surgery and 159 patients were included in the ITT analysis. Patients were required to have a certain degree of pain, assessed as moderate or severe based on their recording in a visual analogue scale, before being randomised. The outcomes showed statistically superior efficacy of all Maxigesic® doses compared with placebo but no difference between the active arms. The dose response curves were shallow, suggesting similar efficacy for all three tested doses of Maxigesic®. However, the standard dose of 4000mg/1200 mg four times a day was superior to the two lower doses in a number of secondary end points, such as the % of responders to reach a 50% pain reduction. Nevertheless, these differences were modest emphasising the potent analgesic effects of Maxigesic® and the wide range of available dosing, adding pain relief flexibility to titrate against the individual's perceived pain. The great majority of patients were randomised suffering moderate pain (150) and only 9 exhibited severe pain which would minimize the sensitivity of the study to separate out the higher doses under the need for more aggressive pain relief in severe pain.

In conclusion the study AFT-MX-3 may give a hint of a “sparing” effect. Thus, the data suggest that in this pain model a dose reduction with retained efficacy is possible.
However, Paracetamol/Ibuprofen Vale contains the maximum dose of paracetamol and a relatively high dose of ibuprofen which becomes the maximum dose recommended/day if given four times daily. Thus, the drug-sparing effect is 100 mg ibuprofen when given as single dose but there is no drug-sparing effect when given four times daily.

Systematic Review of Previously Published Studies
A systematic search was performed to account for the clinical efficacy studies on intravenous paracetamol and ibuprofen in the treatment of postoperative pain associated with minor and major surgery. Searches were made in MEDLINE and EMBASE using a search strategy and selection criteria described in the Appendix, Section 2.5.8. A total of 134 relevant citations were found on MEDLINE and 263 found on EMBASE. Following the removal of 74 duplicates and application of the selection criteria, 96 abstracts were considered to be of relevance to the efficacy of intravenously administered paracetamol and/or ibuprofen in postoperative pain. A further 11 studies pertained to the safety and/or pharmacokinetics of intravenously administered paracetamol or ibuprofen. Additionally, 50 studies examined intravenous paracetamol or ibuprofen in indications other than postoperative pain. These were excluded from the efficacy study, but were included in the safety summary.
The available literature supports the concept that a therapeutic combination of paracetamol and an NSAID may provide improved analgesia than the use of either active ingredient on its own. Two studies were identified that combined paracetamol and ibuprofen with one or both drugs administered by the intravenous route. A further five studies were identified that combined paracetamol with another NSAID. These seven studies are discussed in detail, with a summary of the studies that compared combination therapy to monotherapy. In addition, the administration of paracetamol or

ibuprofen alone via the intravenous route has been studied by a large number of studies, and the results of these studies are briefly summarized, grouped according to the post-operative pain model used to demonstrate analgesic efficacy.

Paracetamol and ibuprofen
One published study has compared co-administration of intravenous paracetamol and ibuprofen with ibuprofen alone in patients undergoing elective knee or hip arthroplasty (Gupta et al., 2016).
In this randomized, single center trial, patients received either paracetamol + ibuprofen (1000 and 800 mg respectively; n = 39) or ibuprofen alone (800 mg; n = 35) from the time of surgery, and every six hours for up to five days. The primary outcome of this study was a difference in VAS pain scores, which was significantly lower in the paracetamol/ibuprofen-treatment group at Day 3. In terms of secondary outcomes, patients receiving the combination treatment required significantly less opioid medications post-operatively (20 mg vs. 25 mg, $p < 0.001$). Combination-treated patients were discharged from the Post-Anesthesia Care Unit earlier (38 minutes vs. 55 minutes) which was not statistically significant ($p = 0.178$) however may be clinically relevant. The quality of recovery, determined on a QoR40 scale was equivalent between treatments.

Another small study investigated the combination of orally administered paracetamol with intravenous ibuprofen or placebo in patients undergoing transsphenoidal surgery for pituitary lesions (Shepherd et al., 2017). This randomized, single center, double-blinded, placebo-controlled trial was stopped early after finding the combination of paracetamol and ibuprofen to be superior for pain relief to paracetamol alone. Patients were administered 1000 mg oral doses of paracetamol every six hours combined with either intraoperative intravenous ibuprofen, which was continued every eight hours (800 mg; n = 28), or intraoperative placebo, which was administered every eight hours (n = 34). The primary outcome of this study was a difference in VAS, which was lower in the combination treatment group than paracetamol-only treated patients (1.7 vs. 3.0, $p < 0.0001$). In addition, opioid use was lower in combination-treated patients (26.3 mg vs. 62.5 mg, $p < 0.0001$). As orally administered paracetamol and intravenous paracetamol are bioequivalent in terms of AUC, the results of this study support the combined administration of intravenous paracetamol and ibuprofen for post-operative pain.

In conclusion it can be said these are the most important two studies within the literature review as they evaluate the effectiveness of the co-administration of paracetamol and ibuprofen.
The study conducted by Gupta et al., from 2016 did not show favourable results. Only on day 3 the VAS pain score was significantly lower in the paracetamol/ibuprofen-treatment. Patients receiving the combination treatment required only minimally (albeit significantly) less opioid medication post-operatively (20 mg vs. 25 mg,). However, the quality of recovery was equivalent between treatments.
The study by Shepherd is more promising but the difference in VAS was 1.3 while at least 2.0 would have been desirable. Nevertheless, opiate use was visibly lower.
Summarised, there appears to be a beneficial effect of the combination therapy which becomes evident in a rescue-medication sparing effect and in variable pain relief on the pain scale which however does not always translate into clinical relevance.

Published Systematic Reviews
No systematic reviews were identified that examine the combination of intravenous paracetamol and intravenous ibuprofen. The systematic literature review only identified one single study which administered both intravenous paracetamol and intravenous ibuprofen (1000 mg and 800 mg, respectively) (Gupta et al., 2016). This clearly indicates the need for further with this combination studies in the future.

Literature Summary
In summary, the systematic reviewed literature demonstrates that intravenous paracetamol and intravenous ibuprofen are effective analgesics in a postoperative pain setting. To date, there are few studies that combine intravenous paracetamol and intravenous ibuprofen. Where studies have combined paracetamol with another NSAID, including ibuprofen, where either or both paracetamol

and ibuprofen have been administered parenterally, combination treatment has been shown to provide superior analgesia and/or have an opioid-sparing effect when compared to the monocomponents (Elseify et al., 2011; Gupta et al., 2016; Mohamad et al., 2014; Salonen et al., 2009; Shepherd et al., 2017). Collectively, these studies support the clinical studies presented by AFT Pharmaceuticals Ltd. in this application that the fixed dose combination of paracetamol and ibuprofen, in the form of Maxigesic® IV, is an effective analgesic for the relief of mild to moderate pain, where an intravenous route of administration is considered clinically necessary.

Overall conclusion on efficacy

Iv paracetamol and iv ibuprofen are effective analgesics in their own rights and the iv combination provides better pain relief. However, the results of the pivotal study, the supporting studies on tablets and the literature review are not unequivocal. The combination therapy appears to have a rescue medication sparing effect and to provide better pain relief but not always to the point of clinical meaningfulness.

The Cochrane publication by Moore, R.A., Derry, S., Aldington, D., and Wiffen, P.J. (2015b). Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews, Cochrane Database Syst Rev CD008659, leaves no doubt on superior efficacy of single dose treatment in postoperative pain of the FDC tablet over the mono-components.

In addition, the CHMP considered benefit-risk balance as adequately demonstrated for Ibuprofen/Paracetamol 500mg/150mg film coated tablets (and associated names fixed dose combination) for the indication mild 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).

Bridging of efficacy and safety of the IV FDC to the FDC tablet was regarded as possible, by in large. However, as the treatment period of pivotal study AFT-MXIV-07 only lasted two days the maximum treatment duration of the applied for IV FDC has also been limited to two days.

Therefore, the applied for product can have its place in the short-term treatment of acute moderate pain up to two days, preferably in clinical scenarios where treatment with the single components is not regarded as sufficient or where an intravenous route of administration is considered clinically necessary and/or when other routes of administration are not possible.

The indication fever had been removed by the Applicant during day 120 because the Applicant had not supplied any supporting data and the clinical study data and literature data available does not show a clinically relevant superior effect of Paracetamol/Ibuprofen compared to the mono treatments with paracetamol or ibuprofen.

IV.5 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 to avoid possible additive side effects on the GI tract, liver, cardiovascular system and renal function.

It should be therefore 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 2-3.2 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 reminder that IV treatment is in general associated with higher rates of AEs compared to perioral application.

The safety data from the pivotal effect and safety study AFT-MXIV-07 presented by the Applicant does not indicate a significantly worse safety profile of the iv-combination therapy compared to the iv

single therapies. However, as the treatment period is conducted over two days the treatment period of the applied for IV FDC-product has also been limited to two days.
K.Brune and B.Hinz indicated that patients on high-dose combination (ibuprofen 400 mg / paracetamol 1000 mg three times a day) lost significantly more blood than those on ibuprofen alone (400 mg three times a day), possibly related to the additional COX-1 inhibition by paracetamol (Munsterhjelm et al, 2005). However, this has been discussed in detail as part of the CHMP referral procedure (EMEA/H/A-29(4)/1447, Doc. Ref EMA/517503/2017) for the oral paracetamol/ibuprofen FDC which concluded on a positive B/R balance.
The potential for increased risk for AKI regarding the combination therapy, especially in the Elderly has been considered. The often-reduced Creatinine Clearance in the Elderly could increase this risk. However, safety of the FDC tablets has been addressed within the CHMP AR mentioned above and the FDC appeared well tolerated in the short treatment of the Elderly. Furthermore, the maximum treatment period for the applied for IV FDC product has been further limited to two days compared to three days of the peroral FDC which is limited to three days.
As always if an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

The results of the retrospective study "Association between an excess risk of acute kidney injury and concomitant use of ibuprofen and acetaminophen in children, retrospective analysis of a spontaneous reporting system" by Zhihua Yue et al. from January 2014 illustrated that the concomitant use of ibuprofen and acetaminophen in children might be associated with increased risk of AKI. However, this study with its many limitations has already been discussed in detail during the CHMP referral procedure for the FDC tablet form which nevertheless resulted in a positive B/R conclusion for treatment against mild to moderate pain in adults up to three days.
The concern that ibuprofen might lead to depletion of glutathione and thereby increase the risk for paracetamol intoxication has been discussed by the applicant in detail and it can be concluded that this effect is unlikely.
The by the RMS as a hypothetical regarded risk of exacerbation of infection by L-cysteine which is part of the formulation of the applied for product can be considered as refuted in the clinical context. There is significant post-marketing data with high annual use of IV paracetamol products containing the same amount of L-cysteine compared to the applied for IV FDC product and there is no indication for an infection-exacerbating effect of these.
The publication by Clemente Plaza et al (2018) and some of the references within the publication suggest a regulatory effect of L-cysteine on activity of the immune system and of the N-acetyl derivate N-acetylcysteine on infection in in-vitro and in animal models.
It has to be taken into account that the maximum treatment period is only two days, i.e. this treatment period is most likely too short for any hypothetical infection-exacerbating effect to take effect.
Furthermore, in line with *EPITT No 19415,* the following warning has been added to section 4.4 of the revised SmPC*:*

Masking of symptoms of underlying infections
/…/ can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When /…/ is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

In conclusion all safety issues have been resolved and the benefit/risk balance of the applied for product is considered positive.

IV.6 Risk Management Plans

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 Paracetamol/Ibuprofen Vale, 10 mg/ml + 3 mg/ml, solution for infusion.

Safety specification
Summary table of safety concerns in RMP version 0.2 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.

IV.7 Discussion on the clinical aspects

The benefit/risk balance is considered positive and Paracetamol/Ibuprofen Vale, 10 mg/ml + 3 mg/ml, solution for infusion, is recommended for approval.

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 application for Paracetamol/Ibuprofen Vale is considered approvable.

The product information is satisfactory.
The benefit/risk ratio is considered positive and Paracetamol/Ibuprofen Vale, 10 mg/ml + 3 mg/ml, solution for infusion, is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Paracetamol/Ibuprofen Vale, 10 mg/ml + 3 mg/ml, solution for infusion, was positively finalised on 2020-04-29.

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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