Summary Public Assessment Report

non-generics

Tachifenekid 32 mg/ml + 9.6 mg/ml oral suspension Paracetamol/Ibuprofen

MT/H/0467/001/DC

Date: 17th January 2025

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Tachifenekid 32 mg/ml + 9.6 mg/ml oral suspension
Paracetamol 32 mg/ml and ibuprofen 9.6 mg/ml oral suspension

This is a summary of the public assessment report (PAR) for Tachifenekid. It explains how Tachifenekid was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Tachifenekid.

For practical information about using Tachifenekid, patients should read the package leaflet or contact their doctor or pharmacist.

What is Tachifenekid and what is it used for?

Tachifenekid contains paracetamol and ibuprofen.

Tachifenekid is used for short-term management of mild to moderate acute pain which is not considered to be relieved by paracetamol or ibuprofen (alone) in children 2-12 years of age.

How does Tachifenekid work?

Paracetamol works to stop the pain messages from getting through to the brain.
Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (or NSAIDs). It relieves pain and reduces inflammation (swelling, redness or soreness).
You must talk to a doctor if your child does not feel better or if they feel worse after 3 days.

How is Tachifenekid used?

The pharmaceutical form of Tachifenekid is oral suspension and the route of administration is oral.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

What benefits of Tachifenekid have been shown in studies?

The company provided its own data on efficacy and safety studies.

What are the possible side effects from Tachifenekid?

For the full list of all side effects reported with Tachifenekid, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Tachifenekid approved?

The Malta Medicines Authority decided that Tachifenekid's benefits are greater than its risks and recommended that it be approved for use.

A risk management plan has been developed to ensure that Tachifenekid is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Tachifenekid, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Tachifenekid

The marketing authorisation for Tachifenekid was granted on 17th August 2021.

The full PAR for Tachifenekid can be found on the website http://medicinesauthority.gov.mt/advanced-search. For more information about treatment with Tachifenekid, read the package leaflet (link)or contact your doctor or pharmacist.

This summary was last updated in 07-2021.

Public Assessment Report

Scientific discussion

Tachifenekid 32 mg/ml + 9.6 mg/ml oral suspension Paracetamol/Ibuprofen

MT/H/0467/001/DC

Date: 17th January 2025

This module reflects the scientific discussion for the approval of Tachifenekid 32 mg/ml + 9.6 mg/ml oral suspension. The procedure was finalised at 07th July 2021. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tachifenekid 32 mg/ml + 9.6 mg/ml oral suspension from Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
The product is indicated for: the short-term management of mild to moderate acute pain which is not considered to be relieved by paracetamol or ibuprofen (alone) in children 2-12 years of age.

A comprehensive description of the indications and posology is given in the SmPC.

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

II. QUALITY ASPECTS

II.1 Introduction

The Pharmaceutical form is Oral suspension, a viscous pink suspension, free from foreign substances and with characteristic strawberry flavour.

The qualitative composition is as follows:
The active substances are: paracetamol 32 mg and ibuprofen 9.6 mg per 1 mL of product.

The other ingredients are: citric acid monohydrate (E330), glycerol (E422), maltitol liquid (E965), Polysorbate 80 (E433), sodium benzoate (E211), sodium citrate dihydrate (E331), sucralose (E955), Vivapur MCG 591P (microcrystalline cellulose and carmellose sodium), xanthan gum (E415), masking flavor, strawberry flavor, sweet flavor, vanilla flavor, and carmine (E120)

The approved container closure system are a 100 mL or 200 mL bottle with a child-resistant closure and a measuring syringe of 5 mL to be used as a dosage delivery device

II.2 2.2 Drug Substance

The active substances are paracetamol and ibuprofen, which are both included in the Ph. Eur. (Paracetamol monograph no. 49 and Ibuprofen monograph no. 721). The CEP procedure is followed for both the drug substances. The latest versions of the CEPs as issued by EDQM have been submitted for both active ingredients, paracetamol and ibuprofen . A suitable declaration of access in relation to the finished product has been provided by each CEP holder.

The control tests and specifications for both drug substances are adequately drawn up. Stability studies have been performed with both drug substances. Re-test periods have been specified in the respective CEPs issued by EDQM (as indicated above).

II.3 Medicinal Product

The development of the product has been adequately described, and the functions of the excipients explained. The excipients have all been adequately justified according to the "Guideline on pharmaceutical development of medicines for paediatric use" EMA/CHMP/QWP/805880/2012 Rev. 2. The formulation development and manufacturing process development has been adequately described.

A description of the manufacturing process and the in-process controls as well as control of critical steps and intermediates has been provided. The manufacturing process described is for a 1500L commercial scale batch. An adequate description of the manufacturing process, IPCs, control of critical steps and intermediates, process validation and holding times have been provided.

The product specifications adequately cover the appropriate parameters for this dosage form. A risk evaluation on the presence of nitrosamines was submitted in the responses and was considered acceptable. A risk assessment on elemental impurities has also been given. Validation of the analytical methods have been presented. Batch analysis has been performed on three industrial scale batches for all manufacturing sites. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up. The shelf-life of 24 months for the drug product, when stored below 25°C is approved. The shelf-life after first opening is 3 months, if the product is stored at or below 25°C.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Paracetamol
Paracetamol is an analgesic and antipyretic agent commonly used for the relief of fever, headaches, and other minor aches and pains. The mechanism by which paracetamol reduces fever and pain is still unclear. It is known that paracetamol reduces the production of prostaglandins and modulates the endocannabinoid system.

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.

Applicant has provided literature suggesting that the combination of paracetamol and ibuprofen is either equivalent or superior to administration of either drug alone as an analgesic. Moreover, although there is evidence that both paracetamol and ibuprofen act at least partly by modulating the activity of COX enzymes, available information does not suggest an increased risk to human subjects from a pharmacodynamic interaction between the two active ingredients.

The primary toxicity associated with paracetamol involves the liver (hepatocellular necrosis). The primary toxicities associated with ibuprofen involve the GI tract (irritation and bleeding), kidney (interstitial nephritis, renal papillary necrosis), and cardiovascular system (hypertension, myocardial infarction, stroke, thrombosis).
Notably, applicant has submitted evidence which do not suggest an increased risk of co-administering repeated daily doses of paracetamol and ibuprofen than administration of either drug alone.

III.2 Pharmacokinetics

Although both paracetamol and ibuprofen are metabolised primarily by the liver, the metabolic pathways are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. Applicant has previously reported that in a study using human liver enzymes, there was no inhibition of CYP enzymes when the drugs were applied in combination. However, this report is lacking and applicant is requested to provide this source of information.

III.3 Toxicology

Applicant has provided two toxicological reports with the aim to study toxicity on the combination product of ibuprofen and paracetamol. The studies were designed to investigate toxicological effects

by paracetamol and ibuprofen in combination to be compared to the administration of either drug alone.
Applicant has provided single-dose and repeat-dose oral toxicity studies with the combination product in adult rats. These were an acute toxicity study in rats (BASi Study 1247-12131) and a 7-Day Oral Toxicity Study of Paracetamol and Ibuprofen Alone and in Combination in Rats (BASi Study 1247-12072).

Single dose toxicity
In the acute toxicity study, co-administration of single oral doses of paracetamol and ibuprofen at a ratio matching that in Maxigesic® and at up to the limit dose for paracetamol (1000 mg/kg) and the MTD for ibuprofen (300 mg/kg) resulted in mild recoverable signs of non-specific toxicity. A greater incidence of staining (porphyrin) was seen in the combination of paracetamol and ibuprofen compared to either drug administered alone.

Repeated dose toxicity
A seven-day oral toxicity study with daily dosing of paracetamol 80 mg/kg and ibuprofen 24 mg/kg, in combination or with either drug alone was submitted. No additional toxicity to the kidneys or gastrointestinal system than when either drugs are administered alone.

Genotoxicity and Carcinogenicity
Neither paracetamol nor ibuprofen is considered to present a genotoxic or carcinogenic hazard to human subjects, and the applicant found nothing in the available information on these drugs to suggest an increased or novel risk of genotoxicity or carcinogenicity with co-administration in the form of Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension.

Reproductive and developmental toxicity
When administered to pregnant rats and rabbits during the period of organogenesis, ibuprofen reportedly does not affect foetal development in either species.
Paracetamol does not affect reproductive performance of mice in a continuous breeding protocol, although throughout gestation and lactation it does result in reduced birth weights and pup growth. Sperm abnormalities have been observed in mice (IARC, 1999).

III.4 Ecotoxicity/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. It can be concluded that Tachifenekid Oral Suspension in the proposed use, does not pose a risk to the environment.

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. A databank of evaluated octanol-water partition coefficients (Log P). http://logkow.cisti.nrc.ca/logkow/search.html; Williams et al, 2009 which cites Syracuse Research Corporation (www.syrres.com/esc/physdemo.htm); Brun et al, 2006	0.46-0.51			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)	0.33	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			Jones et al., 2006; Toxnet HSDB, 2015; ECHA
Ready Biodegradability Test	OECD 301F	57%			The degradation rate of sodium benzoate (manometric test) was in line with OECD 301F criteria (Henschdel et al., 1997).
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 Environment Canada standard method	EC^{50} IC^{25}	134 32	mg/L µg/L	*Scenedesmus subspicatus* *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 Xu et al, 2009 which cites Brown et al., 2007 Brun et al., 2006	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)	0.099	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			(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	*Ceriodaphnia dubia*
Fish, Early Life Stage Toxicity Test/Japanes medaka (*Oryzias latipes*)	Han et al. 2010	NOEC	0.1	µg/L	Reliable with restrictions
Activated Sludge, Respiration Inhibition Test	There is no evidence of any adverse effects of ibuprofen on bacteria in any relevant test systems with microbial biotransformation of ibuprofen having been shown to be significant.				

N/A=Not Analysed

Conclusions on studies:
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Tachifenekid is not expected to pose a risk to the environment.

III.5 Discussion on the non-clinical aspects

In conclusion, the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is approved.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The individual pharmacokinetic characteristics of the single components of Paracetamol and Ibuprofen are well known.

The applicant has conducted three PK studies with the proposed product.

- AFT-MX-14A: Phase 1, single-dose, fasting PK study in adults comparing Paracetamol/ibuprofen suspension with Maxigesic and Combogesic.
- AFT-MX-14B: Phase 1, single-dose, fed PK study in adults comparing Paracetamol/ibuprofen suspension with Maxigesic and Combogesic.
- AFT-MX-12: Phase 2/3 PK-PD study in children 2-12 years undergoing tonsillectomy with or without adenoidectomy.

Study AFT-MX-14a (Comparative bioavailability study in adults, fasting)
In this study the bioavailability of the Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension formulation was compared with Maxigesic® and Maxigesic® 325 (Combogesic) tablets under fasting conditions in healthy adult subjects.

The Paracetamol / Ibuprofen oral suspension was found to be bioequivalent to the Maxigesic 325 tablet, both with respect to paracetamol and ibuprofen. When comparing the oral suspension to the other tablet (Maxigesic, treatment C) the Cmax for paracetamol was a little higher for the suspension compared to the tablet formulation (Cmax 90% CI; 99-134%), while the AUC was within the BE border. For ibuprofen (treatment A vs C) both Cmax and AUC were within the BE border. The slightly higher Cmax for paracetamol is judged not to be of clinically importance, as it is bioequivalent with the other tablet (Maxigesic 325) and as the overall exposure was similar between the suspension and the tablet formulations.

This study shows that the systemic exposure of both paracetamol and ibuprofen following oral administration of the fixed dose oral suspension in the fasted state is expected to be in similar range as for oral tablets containing the fixed dose combination of paracetamol and ibuprofen.

Study AFT-MX-14b (Comparative bioavailability study in adults, fed)
In this study the bioavailability of the Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension formulation was compared with Maxigesic® and Maxigesic® 325 (Combogesic) tablets under fed conditions in healthy adult subjects.

Paracetamol and ibuprofen related pharmacokinetic parameters were compared between the four different treatments under fed conditions and it was found that AUC limits fell within the 80-125%

bioequivalence range for both paracetamol and ibuprofen. For the oral suspension, the Cmax with food for *paracetamol* was approximately 50% and for *ibuprofen* approximately 76% compared to the Cmax in the fasted state. AUC was not affected by food. For the Maxigesic tablet (treatment C) Cmax *paracetamol* with food was approximately 68% and for *ibuprofen* approximately 92% compared to Cmax in the fasted state. AUC was not affected by food. Thus, the oral suspension had a slightly larger negative food effect on the Cmax than the Maxigesic tablet. This is not clinically relevant.

Study AFT-MX-12 (Pharmacokinetic-pharmacodynamic study in children)
This was a randomised, single-blind, parallel group, comparison of the pharmacokinetic profiles, dose response, analgesic effectiveness and safety of a high and low dose of Paracetamol/Ibuprofen Vale, oral suspension fixed-dose combination in children undergoing tonsillectomy with or without adenoidectomy. The primary pharmacokinetic objective was to characterise the pharmacokinetic profile of the two different dose regimens in children between 2-12 years of age. The pharmacokinetic characterisation was conducted following a single loading dose of paracetamol + ibuprofen of either 24 mg/kg + 7.2 mg/kg or 30 mg/kg + 9 mg/kg. A total of 158 children were included in the PK population, of which 71 were in the high dose group and 87 were in the low dose group.

There was no difference in Cmax or AUC for either analyte between age groups (2-6 years vs. 7-12 years) nor between procedure types (tonsillectomy only vs. tonsillectomy and adenoidectomy), however there was a significant difference in both parameters, for both analytes between treatment groups (high dose vs. low dose). The ratio of each of these PK parameters between the high and low dose treatment group ranged from 1.13 – 1.28, consistent with a 25% increase in dose between the low and high dose groups.

The Applicant presented a comparison of the Cmax and Tmax values found in adults (AFT-MX-14) and children (AFT-MX-12) after a single dose of Paracetamol/Ibuprofen Vale oral suspension. The comparison of exposure in children with the exposure in adults dosed with the fixed-dose combination is relevant to extrapolate efficacy and safety data from adults to the paediatric population.

The applicant has provided detailed presentation of the data as seen in simulations. The simulations show that the exposure in children (using the data from AFT-MX-12), when given at the doses proposed by the applicant in the SmPC, are similar to the exposure in adults (using data from AFT-MX-1) with the proposed posology that has been shown in adults to result in an effective and safe exposure (i.e. 500/150 and 1000/300 mg Paracetamol /ibuprofen respectively). The primary PK parameters were AUC and Cmax and single as well as multiple dosing has been investigated for children at different weights/kg and ages.

The applicant submitted plots of observations versus individual and population predictions for both paracetamol and ibuprofen, stratified on weight bands of less than 2kg difference and age. Children were simulated given the amended proposed lower dose of 32mg/ml Paracetamol and 9.6mg/ml Ibuprofen. According to these plots, the model can adequately predict the observed exposure in children 2-12 years of age, across all included weights. Although AUC increases with weight and age, upper dose is capped, resulting in a comparative decrease in AUC in children 41-60 kg. Similarly, Cmax does not change over the age range simulated, except for a comparative decrease in Cmax in children 41-60 kg due to a capped maximum dose.

In addition, as the applicant is simulating the exposure in adults, the applicant showed that the adult model could predict adults observed exposures. This was done in order to confirm that the model could indeed be used for simulation of correct exposure in adults given certain doses.

The applicant provided plots comparing children to adults who received both 500/150 mg and 1000/300 mg paracetamol/ibuprofen. This is appropriate since the approved adults' doses are 1-2 tablets, and in order to show that the children reach an exposure for both compounds that is similar to the exposure in adults this was necessary. The comparative Cmax and AUC were given at the end of each simulation package. The majority of children of all relevant body weights (age 2 to 12 years), with the proposed posology have an exposure (both AUC and Cmax, presented per 1 kg-weight increment) fall within the exposure range that encompasses 90% of the adults (prediction interval or observed range) when given the effective dose of FDC tablet (both 500/150 mg and 1000/300 mg) .

The Pop PKPD model shown in Hannam et al., 2018 has been explored using the data from this product. The full PopPK report has been provided. This is considered to be acceptable. This Pop PK

Model was validated, with prediction corrected VPC's provided, goodness of fit plots as well as weighted residual plots. The same validation was done on the PopPKPD model.

IV.2 Pharmacodynamics

Pharmacotherapeutic group:
Ibuprofen: Anti-inflammatory and antirheumatic products, nonsteroidal; propionic acid derivatives, ATC code: M01AE01
Paracetamol: Anilides, ATC code N02BE01

Paracetamol is a distinct class from NSAIDs. Paracetamol possesses both analgesic and antipyretic properties but is not anti-inflammatory. Originally synthesized in the late 1800s, it was first released for use on prescription in 1955 in the USA and 1956 in the UK. It has been available OTC for many years. It may act via central inhibition of prostaglandin synthesis however it also appears to modulate the endogenous cannabinoid system. It has long had the cachet of being very safe with minimal gastric side effects in contrast to aspirin which was the original alternative analgesic.

Ibuprofen is one of the most commonly used NSAIDs and was the first drug of this class to be approved for OTC use in the UK in 1983 and the USA in 1984.

The proposed combination adds additional analgesic efficacy to each monocomponent while limiting the chances of class-related adverse effects, which are typically dose-related. Combining paracetamol and ibuprofen for the treatment of pain is supported by many clinical studies. In adult and paediatric pain studies, the ratio of paracetamol to ibuprofen appears to impact the additive analgesic effect of combined treatment compared to monotherapy. Higher ratios of paracetamol to ibuprofen show superior analgesia over monocomponents, however as the dose of ibuprofen increases relative to paracetamol, this superiority is lost. The clinical data is supported by modelling, which indicates that when paracetamol is added to ibuprofen at doses lower than 5 mg/kg there is an additive effect, however at doses of ibuprofen exceeding 5 mg/kg, there is minimal benefit from the addition of paracetamol.

IV.3 Clinical efficacy

The clinical documentation on efficacy of the fixed-dose combination product of paracetamol and ibuprofen in children includes an overview of 4 supportive studies.

The Applicant also provided a Systematic Review of Previously Published Studies separately for the treatment of pain and fever and for Alternating Combination Therapy in children and adults. Published Systematic Reviews in children were also discussed in the Clinical Overview.

IV.4 Clinical safety

The safety of Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension was assessed in two studies: a PK study in healthy adults, and a PK-PD study in children aged 2-12 undergoing tonsillectomy with or without adenoidectomy.

Supportive Studies in adults with Maxigesic® and Combogesic® tablets:
A pooled analysis of the four randomized, controlled, multiple-dose clinical studies of the tablet formulations Maxigesic® (paracetamol 500 mg + ibuprofen 150 mg per tablet, 2 tablets per dose, examined in the clinical studies AFT-MX-1, AFT-MX-3, and AFT-MX-6E) and Combogesic® (paracetamol 325 mg + ibuprofen 97.5 mg per tablet, 3 tablets per dose, examined in the clinical study AFT-MX-6) was conducted.

The Applicant also presents a Summary of Safety from Clinical Efficacy Literature which looks

at safety outcomes after treatment with the combination therapy against pain, in particular after Tonsillectomy and/or Adenoidectomy, and after treatment with the combination therapy against fever.
Furthermore literature was reviewed for safety outcomes in alternating combination therapy in the treatment of pain or fever.

For AFT-MX-14, the subjects were closely monitored for AEs during the dosing period. Adverse events were monitored for up to 7 days after the last dose of the study medication by spontaneous reporting and a final follow-up phone call. Similarly, in AFT-MX-12, all AEs were recorded up to 11 days after the first dose of study medicine.

Table 1: Summary of studies submitted in support of the clinical safety of Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension.

Study	Product	Subjects	Safety Outcomes
AFT-MX-14A PK Study (Fasted state)	- Maxigesic® Oral Suspension (1000 mg paracetamol + 300 mg ibuprofen in 31.25 mL) - Maxigesic® Sachet (1000 mg paracetamol + 300 mg ibuprofen) - Maxigesic® tablets, 2 tablets (1000 mg paracetamol + 300 mg ibuprofen) - Maxigesic® 325 tablets, 3 tablets (975 mg paracetamol + 292.5 mg ibuprofen)	26 healthy adult males aged 18-50 with body mass index 18.5-30 kg/m^2	- 1 AE in 1 participant - Well tolerated
AFT-MX- 14B PK Study (Fed state)	- Maxigesic® Oral Suspension (1000 mg paracetamol + 300 mg ibuprofen in 31.25 mL) - Maxigesic® Sachet (1000 mg paracetamol + 300 mg ibuprofen) - Maxigesic® tablets, 2 tablets (1000 mg paracetamol + 300 mg ibuprofen) - Maxigesic® 325 tablets, 3 tablets (975 mg paracetamol + 292.5 mg ibuprofen)	28 healthy adult males aged 18-50 with body mass index 18.5-30 kg/m^2	- No AEs during study - Well tolerated
AFT-MX-12 PK-PD Study	- Maxigesic® Low Dose Oral Suspension (paracetamol 12 mg/kg + ibuprofen 3.6 mg/kg) - Maxigesic® High Dose Oral Suspension (paracetamol 15 mg/kg + ibuprofen 4.5 mg/kg)	251 children aged 2-12 year undergoing tonsillectomy +/- adenoidectomy	- 170 AEs in 111 participants - Well tolerated

Across two clinical studies, at least 279 subjects have been exposed to Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension for up to 11 days of repeated exposure.

Adverse Events
Analysis of Adverse Events
AFT-MX-14A (fasting state)
One participant reported an AE during the study – mild, intermittent toothache one day prior to administration of Maxigesic® 325 tablets. This was considered unrelated to the study drug.
Overall the study drugs were well tolerated.

AFT-MX-14B (fed state)
No AEs occurred during the four study periods. The tolerability of the studied treatments was very good.

AFT-MX-12
In total, 251 subjects received at least one dose of the study medication. Of these, 111 subjects reported 170 AEs. Of the 111 subjects who reported any AEs, 60 subjects (accounting for 90 AEs) were from the high dose group and 51 subjects (accounting for 80 AEs) were from the low

dose group. The number of AEs reported per individual was 0.70 in the high dose group and 0.65 in the low dose group. A Chi-square test was conducted to compare the distribution of AEs by system organ class between the two treatment groups. The p-value was 0.388, indicating no significant difference between the high dose group and low dose group in terms of the percentage of individuals who reported any AEs.
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Common Adverse Events

Gastrointestinal disorders were the most frequently reported AE in AFT-MX-12 (113/170=66.5%), including nausea and vomiting, which affected 10.4% and 23.5% of patients respectively, as well as abdominal discomfort, abdominal pain, constipation, diarrhoea, breath odour, pharyngitis, and acid peptic disease. This was consistent with the observations from previous Maxigesic® tablet studies (AFT-MX-1, AFT-MX-3, AFT-MX-6E and AFT-MX-6). The second most frequently affected system class in children in the present study was injury, poisoning and procedural complications (9.4%), of which most were post-operative bleeding events (12 of 16) or post-operative infections (4 of 16).

Of the 170 AEs reported, 73.5% were considered “mild” (125/170), 24.7% were considered “moderate” (42/170) and 1.8% were considered “severe” (3/170). This was comparable between the high and low dose groups. There were 3 AEs reported as “severe” during the study, all in the low dose treatment group. These AEs were mouth blisters (chicken pox), nausea, and fever, all of which were considered “not related” to the study medication. A Mann-Whitney U test was conducted to compare the distribution of the maximum severity of AEs experienced by each patient between the two treatment groups. The distribution in the severity of AEs was equivalent between the two groups ($p = 0.174$).

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When considering the relationship to the investigational drug, of the 170 AEs reported, 75.9% were considered “not related” (129/170), 15.9% were considered to be “unlikely related” (27/170), 7.6% were considered “possibly related” (13/170), 0.6% were considered “probably related” (1/170) and none were considered “definitely related.” This was comparable between study groups. A Mann-Whitney U test was conducted to compare the distribution of the closest relationship of AEs experienced by each patient to the study medication between the two treatment groups. The distribution in the relationship of AEs was equivalent between the two groups ($p = 0.113$).

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The duration of exposure to the study medication in AFT-MX-12 was longer than is intended for OTC administration of Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension. Despite this prolonged exposure (up to 11 days, mean ± SD duration across both groups: 8.2 ± 3.3 days), the study medication was well tolerated, with most AEs emerging within the first few days post-operatively. Half of all AEs started during the inpatient phase (Day 0, day of surgery), with the number of AEs emerging steadily reducing over the course of the study.

Table 7: Summary of the timing of AE emergence in AFT-MX-12.

Study Day		Low Dose (N=123)	High Dose (N=128)	Total (N=251)
Day 0	N	41	44	85
	%	51.3%	48.9%	50.0%
Day 1	N	10	16	26
	%	12.5%	17.8%	15.3%
Day 2	N	11	6	17
	%	13.8%	6.7%	10.0%
Day 3	N	4	6	10
	%	5.0%	6.7%	5.9%
Day 4	N	2	2	4
	%	2.5%	2.2%	2.4%
Day 5	N	4	3	7
	%	5.0%	3.3%	4.1%
Day 6	N	2	3	5
	%	2.5%	3.3%	2.9%
Day 7	N	2	4	6
	%	2.5%	4.4%	3.5%
Day 8	N	1	2	3
	%	1.3%	2.2%	1.8%
Day 9	N	1	3	4
	%	1.3%	3.3%	2.4%
Day 10	N	2	0	2
	%	2.5%	0.0%	1.2%
Day 11*	N	0	1	1
	%	0.0%	1.1%	0.6%

*One subject reported an AE on Day 11, which was after the cessation of consumption of study medication, but prior to the final Day 11 follow-up call.

Deaths

There have been no deaths in participants taking part in trials with Paracetamol 160 mg/5 mL & Ibuprofen 48 mg/5 mL oral suspension.

Other Serious Adverse Events

There were no serious adverse events (SAEs) in adults in the AFT-MX-14 study.

During the paediatric study AFT-MX-12, a total of 13 SAEs were reported. Of these, 7 SAEs were reported from the high dose group and 6 were reported from the low dose group. Among the 13 SAEs, only 4 SAEs resulted in an early withdrawal during Day 0 and Day 1 (1 from the high dose group and 3 from the low dose group). Of the 13 SAEs, 8 were post-operative bleeding. One of the SAEs was evaluated as being “remotely possibly” related to the study medication while the others were evaluated as “unrelated.”

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2.7.4.2.1.4 Other Significant Adverse Events

In the study AFT-MX-12, there were 9 early withdrawals due to AEs, out of a total of 26 early withdrawals. These are listed below. Among the 9 early withdrawals due to AEs, 5 were from the high dose group and 4 were from the low dose group.

Table 9: Summary of early withdrawals due to AE/SAEs in AFT-MX-12.

Rand. No.	Treatment Group	Reason for EW	Relationship of SAE/AE to investigational drug
05005	High Dose	EW due to SAE on Day 0 (stridor)	Unlikely
07025	Low Dose	EW due to SAE (post-op bleeding on Day 0 after Dose 1)	Not related
07027	High Dose	EW after Dose 2 on Day 1 due to AE (asthma)	Possibly related
07037	Low Dose	EW after Dose 1 on Day 0 Due to SAE (vomiting)	Not related
07042	High Dose	EW due to AE on Day 0 (vomiting)	Possibly related
15005	Low Dose	EW at the end of Day 1 due to AE and SAE (sore stomach and post-op bleeding)	Unlikely related
05041	High Dose	EW on Day 5 due to AE (allergic reaction)	Possibly related
07012	High Dose	EW on Day 8 due to SAE (post-op bleeding)	Not related
13027	Low Dose	EW on Day 6 due to SAE (post-op bleeding)	Not related

AFT-MX-12 set out to compare the incidence of known specific NSAID and paracetamol adverse effects (e.g. GI ulceration and bleeding, indigestion/stomach pain, post-operative bleeding, bronchospasm, water retention, renal failure, skin reactions, thromboembolic events and evidence of clinical hepatitis) up to 11 days after the first dose of study medication. These are described below.

Gastrointestinal Disorders

Gastrointestinal disorders, including nausea, vomiting and stomach ache, were the most frequently reported AEs amongst the two study groups, accounting for 66.5% of all AEs. The percentage of patients experiencing GI disorders was 39.1% in the high dose group and 33.3% in the low dose group.

The majority of these AEs were “mild” to “moderate” in severity. Only one serious GI disorder was reported during the study (SAE 10, subject 07037/TRC), where the subject experienced severe nausea and vomiting which resulted in a prolonged hospital stay. The subject took only one dose of study medication, the loading dose prior to the surgery. This SAE was evaluated as “unrelated” to the study medication and the possible aetiology was “the anaesthesia” for the tonsillectomy surgery.

No GI bleeding/ulceration was reported during the study.

Post-operative Bleeding

Amongst the 170 AEs reported, there were 12 post-operative bleeding events, accounting for 7.1% of AEs. Of the 12 post-operative bleeding events, 8 events were serious and 4 events were non-serious; 7 events occurred in subjects who received the lower dose of study medication and 5 events occurred in subjects who received the higher dose of study medication. Amongst the 8 serious post-operative bleeding events (SAEs), 5 events occurred in subjects who received the lower dose of study medication and 3 events occurred in the subjects who received the higher dose of the study medication.

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occurred in the subjects who received the higher dose of the study medication.

Thromboembolic Events

No thromboembolic events were reported during the study.

Bronchospasm

There were two events of “stridor” reported during the study. One was a serious event (subject 05005/CJM) and one was non-serious (subject 25012/APJ). One event was evaluated as being “unlikely” related to the study medication, and the other was evaluated as “unrelated” to the study medication. The possible aetiology of the serious event was “ET (endotracheal) tube” during the general anaesthesia procedure and the subject had a history of mild asthma. Both subjects received the higher dose of the study medication.
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cation.
There was one incident of asthma during the study (subject 07027/S-G). This event was evaluated as mild and as “possibly related” to the study drug. The subject had received five doses of the study drug, and was allocated to the high dose treatment group. The patient withdrew from the study as a result of the AE. This participant had a medical history of mild asthma.

Table 11: Summary of AEs by age group in AFT-MX-12.

System Organ Class	Low Dose				High Dose				Total			
	2-6 years (N=63)		7-12 years (N=60)		2-6 years (N=63)		7-12 years (N=65)		2-6 years (N=126)		7-12 years (N=125)	
	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients
Cardiac Disorders	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.6%)	0	0 (0.0%)	1	1 (0.8%)	0	0 (0.0%)
Ear and labyrinth disorders	2	2 (3.2%)	1	1 (1.7%)	1	1 (1.6%)	3	3 (4.6%)	3	3 (2.4%)	4	4 (3.2%)
Eye disorders	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.8%)
Gastrointestinal disorders	26	20 (31.7%)	25	21 (35.0%)	27	25 (39.7%)	35	25 (38.5%)	53	45 (35.7%)	60	46 (36.8%)
General disorders and administration site conditions	7	6 (9.5%)	0	0 (0.0%)	2	2 (3.2%)	0	0 (0.0%)	9	8 (6.3%)	0	0 (0.0%)
Immune system disorders	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.6%)	0	0 (0.0%)	1	1 (0.8%)	0	0 (0.0%)
Infections and infestations	1	1 (1.6%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.8%)	0	0 (0.0%)
Injury, poisoning and procedural complications	8	8 (12.7%)	3	3 (5.0%)	2	2 (3.2%)	3	2 (3.1%)	10	10 (7.9%)	6	5 (4.0%)
Metabolism and nutrition disorders	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.6%)	1	1 (1.5%)	1	1 (0.8%)	1	1 (0.8%)
Nervous system disorders	3	3 (4.8%)	0	0 (0.0%)	0	0 (0.0%)	4	4 (6.2%)	3	3 (2.4%)	4	4 (3.2%)
Respiratory, thoracic and mediastinal disorders	4	4 (6.3%)	0	0 (0.0%)	4	4 (6.3%)	2	2 (3.1%)	8	8 (6.3%)	2	2 (1.6%)
Skin and subcutaneous tissue disorders	0	0 (0.0%)	0	0 (0.0%)	2	2 (3.2%)	0	0 (0.0%)	2	2 (1.6%)	0	0 (0.0%)
No. of AEs	51		29		41		49		92		78	
No. reporting any AEs (range)	29 (1-5)		22 (1-4)		29 (1-5)		31 (1-5)		58 (1-5)		53 (1-5)	
% reporting any AEs	46.0%		36.7%		46.0%		47.7%		46.0%		42.4%	
No. of AEs per individual	0.81		0.48		0.65		0.75		0.73		0.62	

Paediatric Patients

In AFT-MX-12, subgroup analysis was conducted to compare the incidence of AEs between age groups (2-6 years vs. 7-12 years). Upon dividing the subjects into two age groups (2-6 years and 7-12 years old), the percentage of subjects reporting AEs was found to be similar across both age groups. The AEs reported by participants in each age group are summarised by system organ class in Table 11.

Post-Marketing Data
The oral tablet formulation (Maxigesic®) has been available in New Zealand, the country of origin, since 2009. From October 2009 to 31st of December 2017 more than 36 million tablets have been sold in Australia, over 37 million tablets in New Zealand, over 45 million tablets in the EU and over 21 million tablets in the UAE. During this timeframe a total 9 adverse drug reactions (ADRs) were reported out of which 5 were classified as Non-serious ADRs and 4 were Serious ADRs, thus confirming the safe and well-tolerated profile of this product.

IV.5 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 Tachifenekid Oral Suspension.

Safety specification
Summary table of safety concerns in RMP version 1.0 dated 5 December 2019 as proposed by the applicant:

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Safety during the first 6 months of pregnancy and breast-feeding.

The safety profiles of ibuprofen and paracetamol are considered well characterised, there are no additional pharmacovigilance activities or additional risk minimisation measures to address the risks identified. It is therefore considered that there should be no important identified risks and no important potential risks items in the summary of safety concerns.

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 submitted Risk Management Plan, version 1.0 signed on 5 December 2019 is considered acceptable.

V. USER CONSULTATION

1) 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 quality, non-clinical and clinical data provided, the application was approved.