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Risk Management Plan

Active substance: Ibuprofen

Version number: 3.0
Reference number: PhV-20141664

DLP: 17-09-2013

Active substance(s) (INN or common name):	Ibuprofen
Pharmaco-therapeutic group (ATC Code):	M01AE01
Name of Marketing Authorisation Holder or Applicant:	Actavis Group PTC ehf.
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Ibuprofen 100 mg/5 ml oral suspension

Author: Date: 10-DEC-2014

Eva Tiper, M.Sc.Pharm
PV Specialist, Safety Evaluation
Pharmacovigilance Drug Safety

Reviewer:

Laura Badica, M.Sc.Pharm
PV Specialist, Safety Evaluation
Pharmacovigilance Drug Safety

Date: 11-DEC-2014

Approval: Date: 12-DEC-2014

Valentina Carpen, M.D.
Senior PV Specialist, Safety Evaluation
Pharmacovigilance Drug Safety

On behalf of: Ilse Sjöholm, M.Sc.Pharm
European QPPV
Pharmacovigilance Drug Safety

PHARMACOVIGILANCE DRUG SAFETY
Actavis Group
Ørnegårdsvej 16
DK-2820 GENTOFTE
Fax: +45 4574 0041
Contact point: Pharmacovigilance@actavis.dk
Single contact point: Adriana Focsaneanu

European QPPV:
Ilse Sjöholm, M.Sc.Pharm
Telephone number: +45 7222 3000
Fax: +45 4574 0041
PhV-QPPV@actavis.com

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Part I: Product Overview

Country and date of first authorisation of ibuprofen by Actavis worldwide: 22-10-1981
Country and date of first launch of ibuprofen by Actavis worldwide: 01-06-1990
Country and date of first authorisation of ibuprofen by Actavis in the EEA: 22-10-1981
Is the product subject to additional monitoring in the EU? No

The table below provides an overview on the update history of each RMP section:

Part	**Module/annex**	**Date last updated for submission (sign off date)**	**Version number of RMP when last updated**
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	09-05-2014	RMP version 2.1
	SII Non-clinical part of the safety specification	Not included	Not included
	SIII Clinical trial exposure	Not included	Not included
	SIV Populations not studied in clinical trials	Not included	Not included
	SV Post-authorisation experience	09-05-2014	RMP version 2.1
	SVI Additional EU requirements for the safety specification	09-05-2014	RMP version 2.1
	SVII Identified and potential risks		RMP version 3.0
	SVIII Summary of the safety concerns		RMP Version 3.0
Part III Pharmacovigilance Plan			RMP Version 3.0
Part IV Plan for post-authorisation efficacy studies		09-05-2014	RMP version 2.1
Part V Risk Minimisation Measures			RMP version 3.0
Part VI Summary of RMP		09-05-2014	RMP version 3.0
Part VII Annexes	ANNEX 2 Current or proposed SmPC/PIL		RMP version 3.0
	ANNEX 3 Worldwide marketing status by country	09-05-2014	RMP version 2.1
	ANNEX 4	NA	NA

Part	Module/annex	Date last updated for submission (sign off date)	Version number of RMP when last updated
	Synopsis of clinical trial programme		
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	NA	NA
	ANNEX 6 Protocols for proposed and ongoing studies in Part III	NA	NA
	ANNEX 7 Specific adverse event follow-up forms	NA	NA
	ANNEX 8 Protocols for studies in Part IV	NA	NA
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	NA	NA
	ANNEX 10 Details of proposed additional risk minimisation activities	NA	NA
	ANNEX 11 Mock up examples	NA	NA
	ANNEX 12 Other supporting data	09-05-2014	RMP version 2.1

Overview of versions:

Version number of last agreed RMP:

NA

Current RMP versions under evaluation:
NA

Products covered by the RMP:

Invented name(s)	Ibuprofen 100 mg/5 ml oral suspension
Authorisation procedure	UK/H/5608/01/DC
Brief description of the product including: • chemical class • summary of mode of action	Ibuprofen is an anti-inflammatory and antirheumatic product, non-steroids; propionic acid derivatives. ATC code: M01AE01 Ibuprofen is a NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. Animal models for pain and inflammation indicate that ibuprofen effectively inhibits the synthesis of prostaglandins. In humans, ibuprofen reduces pain possibly caused by inflammation or connected with it, swelling and fever. Ibuprofen exerts an inhibitory effect on prostaglandin synthesis by inhibiting the activity of cyclo-oxygenase. In addition ibuprofen has an inhibitory effect on ADP (adenosine diphosphate) or collagen-stimulated platelet aggregation.
Indication(s)	
Current	NA
Proposed	• Mild to moderate pain due to sore throat, teething pain, toothache, earache, headache, minor aches and sprains • Fever, including post immunisation pyrexia • Symptoms of colds and influenza
Posology and route of administration	
Current	NA
Proposed	<u>Children over 3 months of age</u> **For post immunisation pyrexia**: One 2.5 ml dose followed by one further 2.5 ml dose 6 hours later if necessary. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor. **For pain, fever and symptoms of cold and influenza**: The daily dosage of ibuprofen oral suspension is 20-30 mg/kg bodyweight in divided doses. Using the oral dosing syringe provided this can be achieved as follows: Infants 3 – 6 months weighing more than 5 kg: One 2.5ml dose may be taken 3 times in 24 hours. Infants 6 - 12 months: One 2.5 ml dose may be taken 3 to 4 times in 24 hours. Children 1 - 3 years: One 5 ml dose may be taken 3 times in 24 hours. Children 4 - 6 years: 7.5 ml may be taken 3 times in 24 hours. Children 7 - 9 years: 10 ml may be taken 3 times in 24 hours.

	Children 10 - 12 years: 15 ml may be taken 3 times in 24 hours. Doses should be given approximately every 6 to 8 hours, (or with a minimum of 4 hours between each dose if required). Infants under 3 months of age or weighing less than 5 kg should not take ibuprofen due to lack of data on safety and efficacy. <u>Duration of treatment</u> For short-term use only Children aged over 6 months: If symptoms persist for more than 3 days, consult your doctor. Children aged under 6 months: If symptoms persist after 24 hours use (3 doses), seek medical advice. For oral administration
Pharmaceutical form(s) and strengths	
Current	NA
Proposed	Oral suspension, 100 mg/5 ml

Part II: Module SI - Epidemiology of the indication(s) and target population

I.1 Epidemiology of the disease

Mild to moderate pain due to sore throat, teething pain, toothache, earache, headache, minor aches and sprains

In a study comprising several EU countries, a total of 51.8 million respondents reported pain (20.9%) or just over one in five of the population 18 years of age and over. Moderate pain was reported by 29.4 million and mild pain by 9.0 million. With respect to frequency with which they had problems with pain, options ranged from daily pain to those who experienced pain once a month or less. Pain prevalence studies have consistently shown the impact of gender with women reporting more pain than men, reporting more severe and persistent pain and reporting pain in more body regions. The prevalence of pain across all pain severity categories increases with age, the results (at least for severe and moderate pain) point to the highest prevalence in the 40 to 59 years of age group. Patterns of medication utilization point to an increased utilization of prescription pain medications with increased pain severity. [1]

In Grøholt EK et al study the total prevalence of headache, abdominal pain and back pain among children 7-17 years of age was 14.9, 8.3 and 4.7%, respectively. The most common pain combination was headache and abdominal pain. Pain was most frequent among girls. The prevalence was slightly higher in low educated or low-income families compared to those of high status. Children living in low educated, low-income, worker families had approximately a 1.4-fold odds of having pain. There was a strong association between the different pain conditions and between pain and other forms of distress in the same child.[2]

Fever, including post immunisation pyrexia

As many as 20% of childhood fevers have no apparent cause. A small but significant number of these patients may have a serious bacterial infection; the risk is greatest among febrile infants and children younger than 36 months, making proper diagnosis and management important. Fever accounts for 10-20% of pediatric visits to health care providers. Patients with no easily identified source of infection have a small but significant risk of a serious bacterial infection. If not recognized and treated appropriately and promptly, this can cause morbidity or mortality

Meningitis, pneumonia, urinary tract infection (UTI), human herpesvirus 6 (HHV-6), and bacteremia are serious etiologies of fever in infants and young children.

Neonates' immature immune systems place them at greater risk of systemic infection. Hematogenous spread of infection is most common in this age group or in patients who are immunocompromised. For these same reasons, infants who have a focal bacterial infection have a greater risk of developing metastatic infection or bacteremia.

Treatment recommendations for children with fever without a focus are based on the child's appearance, age, and temperature.

Treatment with antipyretics is somewhat controversial because fever is a defensive response to infection (Sullivan, 2011). Base the decision to treat a fever without a focus on age, presentation, and laboratory results. If antibiotics are administered empirically, close follow-up is required. Parenteral antibiotics are the drugs of choice.[3]

Symptoms of colds and influenza

The common cold is the most common human disease, and affects people all over the globe. Adults typically have two to five infections annually and children may have six to ten colds a year (and up to twelve colds a year for school children). Rates of symptomatic infections increase in the elderly due to a worsening immune system.

Upper respiratory tract infections, nasal congestion, throat complaints, and cough are responsible for 11% of general practice consultations in Australia. Each year, children suffer about 5 such infections and adults two to three infections. One cross-sectional study in Norwegian children aged 4 to 5 years found that 48% experienced more than two common colds annually.
Transmission of common cold infection is mostly through hand-to-hand contact, with subsequent passage to the nostrils or eyes — rather than, as commonly perceived, through droplets in the air. Common cold infections are mainly caused by viruses (typically rhinovirus, but also coronavirus and respiratory syncytial virus, or metapneumovirus and others). For many colds, no infecting organism can be identified. Although they cause no mortality or serious morbidity, common colds are responsible for considerable discomfort, lost work, and medical costs
Nasal and oral decongestants reduce nasal congestion over 3 to 10 hours, but we don't know how effective decongestants are for longer-term relief (>10 hours).
Vitamin C seems unlikely to reduce the duration or severity of cold symptoms compared with placebo. Antihistamines may slightly reduce runny nose and sneezing, but their overall effect seems small. Some antihistamines may cause sedation or arrhythmias.
Antibiotics don't reduce symptoms overall, and can cause adverse effects and increase antibiotic resistance
Native Americans and Inuit are more likely to be infected with colds and develop complications such as otitis media more often than Caucasians. This may be explained by issues such as poverty and overcrowding rather than by ethnicity. [4]
The World Health Organization estimates that worldwide, annual influenza epidemics result in about 3-5 million cases of severe illness and about 250,000 to 500,000 deaths. The Centers for Disease Control and Prevention (CDC) notes that the often-cited figure of 36,000 annual flu-related deaths was derived from years when the predominant virus subtype was H3N2, which tends to be more lethal than H1N1. In patients without comorbid disease who contract seasonal influenza, the prognosis is very good. However, some patients have a prolonged recovery time and remain weak and fatigued for weeks. Mortality from seasonal influenza is highest in infants and the elderly.
Prevention is the most effective management strategy for influenza. To prevent seasonal flu, CDC recommends routine annual influenza vaccination for all persons aged 6 months or older, preferably before the onset of influenza activity in the community. Public health measures are effective in limiting influenza transmission in closed environments. Patients with influenza generally benefit from bed rest. Most patients with influenza recover in 3 days; however, malaise may persist for weeks. [5]

SI.2 Concomitant medication(s) in the target population

Mild to moderate pain due to sore throat, teething pain, toothache, earache, headache, minor aches and sprains

Considering the nature of the disease, it is expected that the following concomitant medications will frequently be used
Mild pain

- Paracetamol

Moderate-to-severe pain
Morphine is the medicine of choice for the second step, however no information have been identified regarding it`s usage as concomitant medication.

Fever, including post immunisation pyrexia

Considering the nature of the disease, it is expected that the following concomitant medications will frequently be used:

- Antibiotics
- Analgesics [3]

Symptoms of colds and influenza

Considering the nature of the disease, it is expected that the following concomitant medications will frequently be used:

- Antihistaminics
- Nasal and oral decongestants
- Vitamin C

SI.3 Important co-morbidities found in the target population

The indications proposed for Ibuprofen 100 mg/5 ml oral suspension are often encountered in the general population. They may affect population of all ages and therefore no important comorbidities are identified for the concerned target groups.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable as this Module is not required for this type of medicine application.

Part II: Module SIII - Clinical trial exposure

Not applicable as this Module is not required for this type of medicine application.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable as this Module is not required for this type of medicine application.

Part II: Module SV - Post-authorisation experience

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

No actions have been taken by regulatory authorities or by Actavis for safety reasons since the last update of this module.

SV.2 Non-study post-authorisation exposure

SV.2.1 Method used to calculate exposure

Sales data up to the most recent date available giving, the number of kg or number of units sold on the substance, collected from Actavis Sales Data warehouse, are used to estimate the patient exposure. The data are supplemented with sales data of Watson company where available and relevant, for the period before January 2013. Starting with January 2013, sales data are centralised into Actavis Sales Data warehouse.

The patient exposure is calculated using the WHO Defined Daily Dose (DDD) for ibuprofen: 1.2 g.

SV.2.2 Exposure

Exposure to ibuprofen is presented cumulatively, for the period after March 2009, in the table below:

Cumulative (including report period)	EU/EEA region		All countries outside EU/EEA	
Route of administration	Quantity sold (g)	Patient years	Quantity sold (g)	Patient years
Oral	26,98,551000	6161075	1,10,052200	251260.7132

No WHO Defined Daily Dose (DDD) for ibuprofen topical gel is available. The patient exposure is calculated using an estimated dose per patient based on the CCSI. It has been estimated that each patient uses one tube in total. Exposure to ibuprofen in the period and cumulatively is presented in the tables below:

Cumulative (including report period)	EU/EEA region		All countries outside EU/EEA	
Route of administration	Quantity sold (packs)	Patients exposed	Quantity sold (packs)	Patients exposed
Topical	18,103	18,103	0	0

SV.3 Post-authorisation use in populations not studied in clinical trials

Not applicable since Actavis did not conducted any clinical trials on ibuprofen.

SV.4 Post-authorisation off-label use

Actavis did not conduct any observational studies in the post-authorisation phase that would offer information regarding off-label use of ibuprofen within EU.

SV.5 Epidemiological study exposure

Not applicable since Actavis did not conduct any epidemiological studies on ibuprofen, aiming to investigate safety or efficacy concerns, study drug utilisation or measure the effectiveness of the risk minimisation measures. In addition, Actavis was not sent the results of any such epidemiological study undertaken by marketing partners.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for harm from overdose

According to proposed SPC for Ibuprofen 100 mg/5 ml oral suspension, ibuprofen overdose is known to be associated with nausea, vomiting, epigastric pain, or more rarely, diarrhoea. Tinnitus, headache, dizziness, vertigo and gastrointestinal bleeding may also occur. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. Children may also develop myoclonic cramps.

Most of these symptoms are mild reactions that usually are easily treated with appropriate medical care.
Overall, it is evaluated that ibuprofen has a low potential for harm from intentional or accidental overdose.

SVI.2 Potential for transmission of infectious agents

Taking into account the manufacturing process, the nature of materials involved and the drug administration technique, no potential for transmission of infectious agents was identified.

SVI.3 Potential for misuse for illegal purposes

Actavis is not aware of any existing potential for misuse of ibuprofen for illegal purposes.

SVI.4 Potential for medication errors

SVI.4.1 Description of medication errors during the clinical trial programme

Not applicable since no clinical trials have been conducted by Actavis.

SVI.4.2 Preventive measures for the final product(s) being marketed

- Prevention of error due to wrong dose (strength, form, concentration)

Dosing information is provided in SmPC section 4.2 and section 3 of PIL. Ibuprofen oral suspention is approved in one concentration only (100 mg/5mL) which makes the potential for medication error due to wrong concentration low.

- Prevention of error due to wrong route of administration

The product is indicated to be administered oraly only

SVI.4.3 Effect of device failure

The products covered by the RMP do not have any device as an integral part of the administration that could lead to errors in administration

SVI.4.4 Reports of medication errors with the marketed product(s)

The following medication error reports were received in Actavis Pharmacovigilance database until the DLP of this report:

Description of error	**Number of occurrences**	**Analysis of cause**	**Steps taken to prevent**	**Comment**
Accidental drug intake by child	11	No common cause identified	Not needed	Out of the cases identified two cases were fatal. Both cases involved multiple suspect drugs, and in one of
Accidental exposure or	3			

Accidental exposure to product				them the patient had a medical history of heroin abuse, therefore direct causality cannot be accurate assessed. The majority of adverse events reported are in line with the safety knowledge of ibuprofen in conditions of correct administration. Furthermore, there is a larger number of non-serious cases received than serious cases and most of the patients have recovered. Currently, these cases with limited or confounding information provided do not form the basis for including of medications errors as a potential risk for Ibuprofen.
Accidental exposure to product by child	3			
Accidental overdose	16			
Drug administration error	4			
Drug prescribing error	1			
Expired drug administered	2			
Inappropriate schedule of drug administration	3			
Incorrect dose administered	1			
Incorrect drug administration duration	2			
Incorrect drug administration rate	1			
Medication error	14			
Wrong drug administered	1			

Ibuprofen 100 mg/5 ml oral suspension is not marketed yet (the application is ongoing) therefore the cases presented above, reported with unknown brand, are not related to this product.

SVI.5 Potential for off-label use

Actavis evaluates that ibuprofen does not have a significant potential to be used off-label, either in population groups with restricted use or in unauthorised indications.

SVI.6 Specific Paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

No paediatric investigation plan (PIP) is available for ibuprofen

SVI.6.2 Potential for paediatric off-label use

For the products covered by this RMP, the following indications are approved in paediatric population:

Indication	Paediatric population	Product list
• Mild to moderate pain due to sore throat, teething pain, toothache, earache, headache, minor aches and sprains • Fever, including post immu isation pyrexia • Symptoms of colds and influenza	Children age 3 month to 12 years old	Ibuprofen 100 mg/5 ml oral suspension UK/H/5608/01/DC

The indications listed in the (proposed) labelling for the product covered by the RMP are often found in the paediatric population. However the current labelling regarding use in children and the existing safe treatment alternatives for children less than 3 months indicate that the potential for off label use is moderate and does not represent a safety concern.

SVI.7 Conclusions

Safety concerns from this module	
Safety concern	Comment
NA	NA

Part II: Module SVII - Identified and potential risks
Non-ATMP version

SVII.1 Newly identified safety concerns (since this module was last submitted)
Not applicable

SVII.2 Recent study reports with implications for safety concerns
Not applicable

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

Identified risk <Heart failure>

Frequency with 95 % CI	For ibuprofen, the bellow rates of serious coronary heart disease were identified in an observational study to measure the effects of NSAIDs, including naproxen, on risk of serious coronary heart disease were obtained. [6] **Ibuprofen**: Person-years 24 614; Coronary heart disease 339; Rate per 100 person-years 13·77; Adjusted rate-ratio* (95% CI) 1·15 (1·02–1·28) ≥1800 mg: 15 751; 231; 14·67; 1·27 (1·11–1·45) <1800 mg: 8864; 108; 12·18; 0·95 (0·78–1·15)
Seriousness/outcomes	This is a serious, life-threatening condition, with a chronic evolution that requires medical hospitalization and may lead to sequelae. In general, the mortality following hospitalization for patients with heart failure is 10.4% at 30 days, 22% at 1 year, and 42.3% at 5 years. Each rehospitalization increases mortality by about 20-22%.[7]
Severity and nature of risk	Signs and symptoms of heart failure include tachycardia and manifestations of venous congestion (eg, edema) and low cardiac output (eg, fatigue). Breathlessness is a cardinal symptom of left ventricular (LV) failure that may manifest with progressively increasing severity.[7]
Risk groups or risk factors	Hypertension, diabetes, angina, and previous episodes of serious cardiovascular disease
Potential mechanisms	Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients[8]
Preventability	Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moder-

	ate congestive heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy
Potential public health impact of safety concern	According to the American Heart Association, heart failure affects nearly 5.7 million Americans of all ages and is responsible for more hospitalizations than all forms of cancer combined. It is the number 1 cause of hospitalization for Medicare patients.
MedDRA terms	NA

Identified Risk <Myocardial infarction>	
Frequency with 95 % CI	A significantly increased risk of myocardial infarction was associated with use of ibuprofen (1.24, 1.11 to 1.39) in a nested case-control study, comprising 9 218 cases. [9]
Seriousness/outcomes	This is a serious, life-threatening condition, with a chronic evolution that requires medical hospitalization and may lead to sequelae. One third of patients who experience MI die within 24 hours of the onset of ischemia, and many of the survivors experience significant morbidity. Acute myocardial infarction is associated with a 30% mortality rate; half of the deaths occur prior to arrival at the hospital. An additional 5-10% of survivors die within the first year after their myocardial infarction. Approximately half of all patients with a myocardial infarction are rehospitalized within 1 year of their index event.[10]
Severity and nature of risk	Patients with typical myocardial infarction may have the following prodromal symptoms in the days preceding the event (although may occur suddenly, without warning): • Fatigue • Chest discomfort • Malaise
Risk groups or risk factors	Atherosclerosis is the disease primarily responsible for most acute coronary syndrome (ACS) cases. Approximately 90% of myocardial infarctions result from an acute thrombus that obstructs an atherosclerotic coronary artery. Poorer prognosis is associated with the following factors: • Increasing age • Diabetes • Previous vascular disease (ie, cerebrovascular disease or peripheral vascular disease) • Elevated Thrombolysis in Myocardial Infarction (TIMI) risk score for unstable angina/NSTEMI (7 factors: Age ≥65 y, ≥3 risk factors for cardiac disease, previous coronary disease, ST segment deviation ≥0.5 mm, ≥2 episodes of angina in last 24 h, aspirin use within prior wk, and elevated cardiac enzyme levels)[• Delayed or unsuccessful reperfusion • Poorly preserved left ventricular function (the strongest predictor of outcome) • Evidence of congestive heart failure (Killip classifi-

Identified Risk <Myocardial infarction>	
	cation ≥II)or frank pulmonary edema (Killip classification ≥III) • Elevated B-type natriuretic peptide (BNP) levels • Elevated high sensitive C-reactive protein (hs-CRP), a nonspecific inflammatory marker • Secretory-associated phospholipase A2 activity is related to atherosclerosis and predicts all-cause mortality in elderly patients; it also predicts mortality or MI in post-MI patients
Potential mechanisms	By decreasing the vasodilatatory and antiaggregatory prostaciclyn production, COX 2 inhibitors may have prothrombotic activity. [11]
MedDRA terms	NA

Identified Risk <Cerebrovascular accident>	
Frequency with 95 % CI	Out of 46 456 patient years (exposure to ibuprofen), the Incidence Density Ratio of cerebrovascular accident (95% CI) was 1.12 (1.05–1.24). This was a retrospective cohort study among veterans ≥65 years prescribed an NSAID or a COX-2 selective NSAID and comprised 384 322 patients. [12]
Seriousness/outcomes	This is a serious, life-threatening condition, with a chronic evolution that requires medical hospitalization and may lead to sequelae. In the Framingham and Rochester stroke studies, the overall mortality rate at 30 days after stroke was 28%, the mortality rate at 30 days after ischemic stroke was 19%, and the 1-year survival rate for patients with ischemic stroke was 77%. However, the prognosis after acute ischemic stroke varies greatly in individual patients, depending on the stroke severity and on the patient's premorbid condition, age, and poststroke complications.[13]
Severity and nature of risk	Common stroke signs and symptoms include the following: abrupt onset of hemiparesis, monoparesis, or (rarely) quadriparesis, hemisensory deficits, monocular or binocular visual loss, visual field deficits, diplopia, dysarthria, facial droop, ataxia, vertigo (rarely in isolation)
Risk groups or risk factors	Nonmodifiable risk factors include the following (although there are likely many others): age, race, sex, ethnicity, history of migraine headaches, fibromuscular dysplasia, and heredity. Modifiable risk factors include the following: hypertension (the most important), diabetes mellitus, cardiac disease:, hypercholesterolemia, tias, carotid stenosis, hyperhomocystinemia, lifestyle issues, oral contraceptive use/postmenopausal hormone use.
Potential mechanisms	By decreasing the vasodilatatory and antiaggregatory prostaciclyn production, COX 2 inhibitors may have prothrombotic activity.[11]
Preventability	Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention, hyperten-

Identified Risk <Cerebrovascular accident>	
	sion and oedema have been reported in association with NSAID therapy
Potential public health impact of safety concern	According to the World Health Organization (WHO), 15 million people suffer stroke worldwide each year. Of these, 5 million die, and another 5 million are left permanently disabled.
MedDRA terms	NA

Identified Risk < Gastro-intestinal bleeding, ulceration, and perforation>	
Frequency	In a review, Michels et al evaluated twenty studies (nine observational, ten clinical trials, one meta-analysis) reporting incidence rates and proportions of a GI bleeding-related event associated with OTC or OTC-specific doses of ibuprofen. The frequency of a GI-related hospitalization was <0.5% across all doses of ibuprofen; OTC-comparable doses had a frequency less than 0.2%. Incidence rates (rates per 1000 patient-years) demonstrated the same trend, with low rates for any dose of ibuprofen and the lowest rates among those using OTC-comparable doses (0 per 1000 patient-years to 3.19 per 1000 patient-years)[14]
Seriousness/outcomes	Theess are serious conditions, with a chronic evolution that requires medical care and may lead sequelae.
Severity and nature of risk	Signs and symptoms of acute upper GI bleeding include the following: hematemesis, melena, hematochezia, syncope, presyncope, dyspepsia, epigastric pain, heartburn, diffuse abdominal pain, dysphagia, weight loss and jaundice. Acute GI bleeding is a potentially life-threatening abdominal emergency that remains a common cause of hospitalization.[15]
Background incidence/prevalence	The relative risk of any GI bleeding-related event ranged from 1.1 to 2.4 for users of OTC-specific doses of ibuprofen compared to non-users; the relative risk among users of any dose of ibuprofen ranged from 1.7 to 2.4 compared to non-users.
Risk groups or risk factors	The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly
Potential mechanisms	NSAIDs cause mucosal damage, ulceration and ulcer complication throughout the gastrointestinal tract by inhibiting prostaglandin synthesis. Prostaglandins are central in the protection against a wide variety of luminal insults.[16]
MedDRA terms	NA

Identified Risk < Exacerbation of Ulcerative Colitis and Crohn's disease>	
Seriousness/outcomes	Theess are serious conditions, with a chronic evolution that requires medical care and may lead sequelae.
Severity and nature of risk	Patients with Ulcerative cholitis predominantly complain of the following: rectal bleeding, frequent stools, sometimes severe diarrhea and cramps, fever, leukocytosis, abdominal distention.[17] The characteristic presentation in Crohn disease is ab-

Identified Risk < Exacerbation of Ulcerative Colitis and Crohn's disease>	
	dominal pain and diarrhea, which may be complicated by intestinal fistulization or obstruction. Unpredictable flares and remissions characterize the long-term course[18]
Risk groups or risk factors	Boner et al observed that the use of low-dose NSAIDs was not associated with an increase in disease activity for these outpatients with either Crohn`s diseanse (CD) or ulcerative cholitis (UC). Use of high-doses of NSAIDs was associated with a higher numerical disease activity index score among CD patients with colonic involvement, but this was not reflected by an increase in significant disease flares.[19]
Potential mechanisms	The mechanism of NSAID injury in Infamatory bowel disease (IBD) is unclear, but a suspected contributing factor is inhibition of colonic prostaglandin synthesis by NSAIDs. NSAIDs inhibit prostaglandin synthesis through both the COX-1 and COX-2 isoforms of cyclooxygenase. COX-1 is expressed in many tissues and is involved in maintaining mucosal integrity in the gastrointestinal tract. COX-2 is expressed at sites of inflammation, including experimental colitis and ileitis. COX-2 expression has additionally been found in inflamed ileum and colon in patients with IBD
Potential public health impact of safety concern	Ulcerative colitis may result in disease-related mortality. However, overall mortality is not increased in patients with ulcerative colitis, as compared with the general population.
MedDRA terms	NA

Identified Risk < Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis) >	
Frequency	According to a review by Rainsford on the pharmacology, efficacy and safety of ibuprofen there have been occasional reports of Stevens-Johnson and Lyell's syndromes as well as severe bullous reactions. However, these serious conditions have not been reported in controlled trials or literature on OTC events from ibuprofen.[20] In a review by Ward et al it is stated that the risk of SJS or TEN caused by NSAIDs is extremely low, less than 1 per 1 million users per week, based on case-control studies and estimates of incidence[21]
Seriousness/outcomes	Theese are serious, sometimes fatal reactions that require hospitalization. The mortality rate for exfoliative dermatitis approaches 30%. .SJS/TEN are of major concern because of severe morbidity and high mortality rates reported from less than 10% in SJS patients to more than 40% in TEN patients (overall 20–25%).[22]
Severity and nature of risk	Exfoliative dermatitis, or erythroderma, is an erythematous, scaly dermatitis involving most, if not all, of the skin. SJ and TEN diseases are characterized by fever, large areas of detachment of necrotic epidermis and erosions of mucous membrane.
Risk groups or risk factors	Several factors are identified to have an impact on the

Identified Risk < Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis) >	
	mortality: age, severity of reaction, recent malignancy, and pre-existing severe kidney or liver disorder, as well as recent infection.
MedDRA terms	NA

Identified Risk < Renal toxicity/ renal failure>	
Frequency with 95 % CI	Huerta et al study that evaluated NSAIDs drugs and risk of acute renal failure (ARF) in a case control study with an initial number of 386,916 patients. The risk for acute renal failure among current single users of individual NSAIDs was examined and ibuprofen accounted for 29% of NSAID use, and RR was 2.6 (95% CI, 1.0 to 6.9) in Huerta et al study that evaluated NSAIDs drugs and risk of acute renal failure (ARF) in a case control study with an initial number of 386,916 patients.[23]
Seriousness/outcomes	Theese are serious, sometimes fatal reactions that require hospitalization.
Risk groups or risk factors	Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, those taking diuretics and and the elderly. There is a risk of renal impairment in dehydrated children and adolescents
Potential mechanisms	Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients
Preventability	In patients with mild or moderate reduction of renal function, the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored. Monitoring of renal function is necessary, especially in high risk patients
MedDRA terms	*NA*

Identified Risk < Use during third trimester of pregnancy>	
Seriousness/outcomes	The reactions to foetus and mother after ibuprofen administration in third trimester are serious, sometimes life threatening.
Severity and nature of risk	During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to: - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); - renal dysfunction, which may progress to renal failure with oligo-hydramniosis; the mother and the neonate, at the end of pregnancy to: - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses. - inhibition of uterine contractions resulting in delayed or prolonged labour
Preventability	Ibuprofen should not be administrated in the last trimester of pregnancy.
MedDRA terms	NA

Identified Risk < Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin>	
Seriousness/outcomes	This is a serious, life-threatening condition, which that sometimes requires hospitalization
Potential mechanisms	NSAIDs and acetylsalicylic acid inhibit the same COX-enzymes, and thus may interact. COX-1 affinity determines the interaction between NSAIDs and ASA on thrombocyte adhesion and aggregation[24]
Preventability	Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low-dose acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk
MedDRA terms	NA

Identified Risk < Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)>	
Frequency	Raddack and Deck conducted a three-week, parallel-group clinical trial involving 41 patients with a mean age of 52 years receiving treatment with at least two antihypertensive drugs, and distributed into three groups (ibuprofen 600 mg every 12 hours, paracetamol or placebo). The results showed the ibuprofen group to experience a significant increase in blood pressure in comparison with the other two groups.
Seriousness/outcomes	This is an interaction with serious consequences that requires medical care.
Severity and nature of risk	The blood pressure increment that may result from such drug interactions increases the risk of acute myocardial infarction and of coronary disease among hypertensive patients by 45-67% (7,23) and 15%, respectively.
Risk groups or risk factors	Normally more than 4-5 days of treatment with both drugs are needed for interactions to manifest. However, even with short periods of treatment, interactions are possible - particularly in more susceptible individuals such as the elderly, patients with congestive heart disease, and hypertensive patients with low renin concentrations.[25]
Potential mechanisms	Inhibition of the enzyme cyclooxygenase, thereby inhibiting the synthesis of inflammatory prostaglandins and vasodilatory prostaglandins that increase renal blood flow and thus favor the excretion of water and sodium. More than five days of treatment with both drugs are normally required for the interaction to manifest.[25]
Preventability	Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter
Potential public health impact of safety concern	Although the changes in blood pressure resulting from this interaction are typically small, some patients can experience substantial elevations in both systolic and diastolic blood pressure. It has been estimated that the avoidance of minor changes in systolic pressure in patients with osteoarthritis subjected to treatment with non-steroidal antiinflammatory drugs would avoid over 30,000

Identified Risk < Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)>	
	deaths due to myocardial infarction, and over 2000 deaths due to coronary disease, in the United States alone.
MedDRA terms	NA

Identified Risk <Use in elderly>	
Seriousness/outcomes	The reactions that may occur in this population, are serious, sometimes life threatening, and may generate sequels.
Severity and nature of risk	Elderly patients are more prone to adverse events and are at increased risk of potentially fatal gastrointestinal, ulceration or perforation haemorrhage (which may be fatal)
Preventability	If treatment is considered necessary, the lowest dose for the shortest duration necessary to control symptoms should be used. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.[8]
MedDRA terms	NA

Identified Risk < Use by patients with (history of) bronchial asthma>	
Seriousness/outcomes	Possible reactions occurred when used in this population makes this risk sometimes life threating, requiring hospitalization. The inflammatory pathogenesis of asthma, anti-inflammatory effect of ibuprofen and evidence suggesting ibuprofen may reduce morbidity in children with asthma raises the intriguing possibility that ibuprofen might actually have therapeutic benefit for at least some children with asthma.[26]
Severity and nature of risk	Increased risk of acute bronchospasm
Potential mechanisms	NSAIDs are commonly avoided by patients with aspirin-induced asthma based on the premise that there is a significant cross-reactivity between aspirin and other NSAIDs
MedDRA terms	NA

Identified risk < Hypersensitivity reactions>	
Frequency	Non-steroidal anti-inflammatory drugs are the second most common cause of drug induced hypersensitivity reactions with prevalence between 0.1% and 0.3%.[28] Cutaneous reactions secondary to NSAID use may affect around 0.3% of the general population. NSAID-induced hypersensitivity reactions have a higher incidence in asmathic patients ranging from 4.3% to 11%. [29]
Seriousness/outcomes	NSAID-induced hypersensitivity reactions are divided into allergic hypersensitivity reactions (immediate reactions and delayed reactions) and non-allergic hypersensitivity reactions. Immediate reactions comprise urticaria, angioedema and allergic anaphylaxis all of which are mediated via immunoglobulin E. The latter complications depending on the severity may be considered life-threatening events that require hospitalization and supportive measures. Delayed reactions comprise serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epider-

Identified risk < Hypersensitivity reactions>	
	mal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.[8] Non-allergic hypersensitivity encompasses manifestations at the respiratory tract and skin, and non-allergic anaphylaxis.[28-29] These may all evolve into serios life-threatening events that mai require hospital admission and supportive care. Hypersensitivity reactions (e.g urticaria, pruritus, and exanthema as well as asthma attacks and hypotension) are listed in the Company Core Safety Information for ibuprofen as uncommon adverse events, whilst sevre hypersensitivity reactions such as facial oedema, swelling of the tongue, internal laryngeal swelling, dyspnoea, tachycardia, fall of blood pressure (life-threatening shock) are listed as very rare events.[8]
Severity and nature of risk	A wide variety of clinical manifestations for hypersensitivity reactions can be produced by NSAIDs and these range from mild events to life-threatening clinical pictures.
Background incidence/prevalence	Drug-induced hypersensitivity reactions account for about one sixth of all adverse drug reactions [28-29]
Risk groups or risk factors	Risk factors include hypersensitivity to ibuprofen or any of the excipients, previous hypersensitivity episodes on administration of NSAIDs or aspirin, prevous asthma attacks, bronchial asthma, nasal polyps, chronic urticaria etc. [8,28-29]
Potential mechanisms	NSAID-induced inhibition of cyclooxygenase causes a net decrease in the synthesis of protective prostaglandin production and this renders the activation of mediator release from inflammatory cells to target tissues leading to local and systemic generation of cystenyl leukotrienes. Abnormalities of lipooxygenase have also been detected in hypersensitivity reactions with increased levels of urinary leukotrienes and upregulation of LTC4 synthase or cystenyl LT receptors.[28-29]
Preventability	Avoid administration of NSAIDs in patients with a previous medical history of asthma, bronchial asthma, nasal polyps, chronic urticaria etc. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. [8]
Impact on individual patient	NSAID induced hypersensitivity reaction is an umbrella term for symptoms that range in severity from mild to life threatening events. Patients are affected at an individual level and should therefore be assessed and managed according to their medical needs.

Identified Risk < Hypersensitivity to NSAIDs or aspirin>	
Frequency	Non-steroidal anti-inflammatory drugs are the second most common cause of drug induced hypersensitivity reactions with frequencies between 0.1% and 0.3%.[28] Cutaneous reactions secondary to NSAID use may affect around 0.3% of the general population. NSAID-induced hypersensitivity reactions have a higher incidence in asmathic patients ranging from 4.3% to 11%. [29]
Seriousness/outcomes	Pre-existing NSAID hypersensitivity manifesting with upper and lower airway disease is referred to as the asthma triad, Widal's syndrome, Samter's syndrome, aspirin-induced asthma etc. Clinical manifestations of aspririn or NSAID exacerbated respiratory disease include nasal congestion, watery rhinorrhoea, shortness of breath and progressive bronchial obstruction. Respiratory signs and symptoms are usually accompanied by additional systemic involvement such as ocular, cutaneous and gastric adverse events. [8,28,29]
Severity and nature of risk	As previously mentioned, symptoms range from rhinorrhoea to severe bronchial obstruction and patients should be managed on an individual level depending on the medical needs. [8,28,29]
Background incidence/prevalence	According to the Company Core Safety Information ibuprofen is contraindicated in patients with prior hypersensitivity to aspirin or other NSAIDs thus the incidence in this patient population cannot be established. In the general population, drug-induced hypersensitivity reactions account for about one sixth of all adverse drug reactions. Nonsteroidal anti-inflammatory drugs have been reported to be the second most common cause of drug-induced hypersensitivity reactions. [28-29]
Risk groups or risk factors	Risk factors include prior hypersensitivity reactions to aspirin and other NSAIDs.
Potential mechanisms	Inhibition of cyclooxygenase results in a net inhibition of protective prostaglandins and triggers the inflammatory response mechanisms that cause respiratory symptoms. Suppression of PGE2 may cause the activation of the inflammatory cascade and render an increase of cystenyl leukotrienes production in the systemic circulation and upregulation of the cystenyl leukotriene receptors in the airway tissue. Genetic polyomorphisms have also been linked to NSAID- exacerbated respiratory disease. [8,28-29]
Preventability	Patients with a medical history of hypersensitivity to NSAIDs or aspirin should not be prescribed ibuprofen. There are useful diagnosis tools in order to detect NSAID-induced hypersensitivity such as skin testing (involves the application of different dilution of NSAIDs on the skin), oral provocation test (oral challenge with aspirin or other NSAIDs) or measurement of specific IgE in serum.[8,28-29]
Impact on individual patient	NSAID induced hypersensitivity reaction is an umbrella term for symptoms that range in severity from mild to life threatening events. Patients are affected at an individual level and should therefore be assessed and managed according to their medical needs. Patients who cannot take

Identified Risk < Hypersensitivity to NSAIDs or aspirin>	
	NSAIDs as needed for pain relief are usually prescribed paracetamol or opoiods in more severe cases.

Identified Risk <Hepatic disorders>	
Frequency	Idiosyncratic, clinically apparent liver injury due to ibuprofen is estimated as a very rare event (with a prevalence of 1.0-1.6 cases per 100,000 prescriptions). ALT elevations usually around 100 U/L have been found on chronic ibuprofen therapy with high doses of 2.4 g-3.6 g of ibuprofen daily. On the other hand, upon chronic adminsitration od placebo, AST levels were comparable to placebo. [30-31]
Seriousness/outcomes	Clinically apparent liver injury during long-term or chronic ibuprofen therapy has not been established, however, cases of asymptomtic flares of chronic hepatitis C have been reported after initiation of ibuprofen therapy with ALT levels rising to more than 1000 U/L and rapidly resolving with stopping.[30-31]
Severity and nature of risk	Ibuprofen-induced liver injury is rare and symptoms are generally mild, however several cases reporting acute liver failure and subsequent death have been published in the literature. [30-31]
Background incidence/prevalence	Drug-induced liver injury has an annual prevalence of 10 to 15 cases per 10,000 to 100,000 patients exposed. Drug-induced liver injury accounts for about 10% of all cases of hepatitis and it is the most prevalent cause for acute hepatitis in the US.[30-31]
Risk groups or risk factors	Risk factors for drug induced liver injury include gender (women are more susceptible than men), alcohol abuse, certain medications (rifampicin, chemotherapy etc), alcohol abuse, malnutrition, paracetamol toxicity etc.[30-31]
Potential mechanisms	The mechanisms of drug-induced liver impairment are yet to be understood, however at the moment it is believed that liver damage occurs via a complex mechanisms involving both toxic metabolic by-products and immunoallergic responses. [30]
Preventability	Use of ibuprofen in patients with previous liver impairment is contraindicated. Ibuprofen should be stopped upon first signs and symptoms of hepatic damage.[8,30,31]

Identified Risk < Aseptic meningitis in patients with SLE and mixed connective tissue disease>	
Frequency	The frequency of drug-induced aseptic meningitis is unknown. Four classes of drug have been associated with drug induced aseptic meningitis, namely NSAIDs, antibiotics, immunosuppressive therapy and antiepileptic medication.[32]
Seriousness/outcomes	Aseptic meningitis is not considered a life-threatening adverse reaction following therapy with ibuprofen. Rates of mortality and morbidity are low and a full recovery from the undersirable event is expected within two weeks from the onset of the reaction. [32]
Severity and nature of risk	Patients who have drug-induced aseptic meningitis typi-

Identified Risk < Aseptic meningitis in patients with SLE and mixed connective tissue disease>	
	cally present with fever, headache, and nuchal rigidity. Signs and symptoms usually appear within 24 to 48 hours after drug ingestion. Drug-induced aseptic meningitis may develop in a patient who initially was able to tolerate the causative drug. In patients who have drug-induced aseptic meningitis, the typical CSF profile reveals a neutrophilic pleocytosis, with several hundred to several thousand white blood cells. Patients who have drug-induced meningitis may have eosinophils present in the CSF (fewer than 5%).[32]
Risk groups or risk factors	Connective-tissue diseases, in particular systemic lupus erythematosus, appear to be a risk factor for drug-induced aseptic meningitis.[32]
Potential mechanisms	There are two proposed mechanisms for drug-induced aseptic meningitis. The first mechanism is a direct chemical irritation of the meninges by intrathecal agents. The second, which applies to nonintrathecal medications, is not as well understood and is presumably a hypersensitivity reaction to the drug (type III or IV). It is based on the assumption that drug-induced aseptic meningitis is an acute hypersensitivity reaction involving the meninges and is supported primarily by circumstantial evidence that includes the temporal relationship between drug ingestion and development of symptoms, the progressively shorter incubation periods in recurrent cases, the development of classic hypersensitivity features, and the rapid resolution of symptoms after the drug is discontinued.[32]
Preventability	Ibuprofen should be used with caution in patients diagnosed with SLE or mixed connective tissue disease.[32]

Identified Risk <Premature closure of the foetal ductus arteriosus>	
Frequency	The incidence of closure of the ductus arteriosus in the general population in the United States ranges from 0.02% and 0.006% of all live births. The prevalence of closure of the ductus arteriosus increases in babies born prematurely occuring in about 20% in premature infants older than 32 week gestation and in about 60% in those younger 28 week gestation.[33]
Seriousness/outcomes	The outlook of the premature closure of the foetal ductus arteriosis is very promising in newborn babies with no other underlying medical conditions.[33-35]
Severity and nature of risk	Signs and symptoms of in utero closure of the ductus arteriosus include tachycardia, systolic thrill, heart murmurs.[34]
Background incidence/prevalence	The prevalence of patients experiencing patent ductus arteriosus in the US ranges from 0.02% to 0.006% of all live births.[34]
Risk groups or risk factors	This incidence increases in babies born prematurely before 28 weeks gestation up to a maximum of 60 cases per 100 live births. Other risk factors for acquiring PDA include possible history of perinatal asphyxia, low birth weight and births at high altitude.[34]

Identified Risk <Premature closure of the foetal ductus arteriosus>	
Potential mechanisms	The foetal respiratory integrity depends on the production of maternal prostaglandins, namely PGE2 and prostacyclin which are the most important mediators of vasorelaxation of the foetal ductus arteriosus. Upon administration of ibuprofen, production of such protective prostaglandins is suppressed resulting in the intrauterine closure of the foetal ductus arteriosus.[35]
Preventability	Avoid administration of NSAIDs during pregnancy. [33-35]
Impact on individual patient	NSAID administration during pregnancy may pose a great health burden on the offspring causing multiple system disorders such as respiratory disorders, reduction of renal function and inhibition of platelet aggregation. Impairment of the respiratory function with constriction of the foetal ductus arteriosus may cause persistent pulmonary hypertension in the neonate and persistent foetal circulation. This is usually reversible in 24 hours upon cessation of NSAID therapy.[35]

Potential Risk <Impaired female fertility>	
Seriousness/outcomes	Impaired female fertility is reversible on withdrawal of treatment
Potential mechanisms	Inhibition of ovulation[8]
Preventability	In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered
MedDRA terms	*NA*

Potential Risk <Medication Overuse Headache>	
Seriousness/outcomes	This is a mild condition, with a chronic evolution that requires medical care.
Risk groups or risk factors	Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen.
Preventability	Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor
MedDRA terms	NA

Potential Risk < Use during 1st and 2nd trimester of pregnancy>	
Severity and nature of risk	Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.
Risk groups or risk factors	The risk is believed to increase with dose and duration of therapy[8]

Potential Risk < Use during 1st and 2nd trimester of pregnancy>	
Potential mechanisms	Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development.
MedDRA terms	NA

Potential Risk < Second myocardial infarction after treatment with ibuprofen>	
Frequency	Of 83,677 patients which had been hospitalised and subsequently discharged in Denmark for a first episode of MI, 42.3% received at least one prescription for a NSAIDs during follow-up, and there were 35 257 death and myocardial infarctions (42.1%) and 29 234 deaths (35.0%) registered during the observation period. The results of this study suggest that diclofenac is associated with a high level of risk, in contrast to the other drugs, from the beginning of the treatment
Seriousness/outcomes	This is serious, life threatening event, that require hospitalisation
Severity and nature of risk	Patients with typical myocardial infarction may have the following prodromal symptoms in the days preceding the event (although may occur suddenly, without warning): • Fatigue • Chest discomfort • Malaise
Potential mechanisms	By decreasing the vasodilatatory and antiaggregatory prostaciclyn production, COX 2 inhibitors may have prothrombotic activity
MedDRA terms	NA

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Ibuprofen is metabolised in the liver (hydroxylation, carboxylation). The elimination half-life is approximately 2.5 hours in healthy individuals. Pharmacologically inactive metabolites are mainly excreted (90%) by the kidneys but also in bile. Ibuprofen`s potential for drug interaction is recognised for the following group of substances:

- Other NSAIDs:
- Anti-coagulants:
- Methotrexate
- Llithium
- Diurectis, beta blockers and antihypertensives
- Selective serotonin reuptake inhibitors (SSRIs)
- Aminoglycosides
- Mifepristone
- Tacrolimus
- Zidovudine
- Quinolone antibiotics
- Sulphonylureas
- Cholestyramine
- CYP2C9 inhibitors (voriconazole, fluconazole)
- Ciclosporine
- Corticosteroids
- Anti-platelet aggregation agents[8]

Of the above, two important identified drug interactions have been recognised:
- Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin
- Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)

SVII.4.2 Important identified and potential interactions

Interacting substance(s): corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin	
Effect of interaction	increase the risk of bleeding and ulceration
Possible mechanisms	protein binding displacement
Discussion	Considering all data available, this safety concern is recognised as an important identified risk

Interacting substance(s): Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)	
Effect of interaction	reduced effect of diuretics and antihypertensive
Possible mechanisms	sodium and water retention, suppression of plasma renin activity, alterations in adrenoceptor sensitivity and impaired synthesis of vasodilator prostaglandins
Discussion	Considering all data available, this safety concern is recognised as an important identified risk

SVII.5 Pharmacological class effects

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

The following safety concerns recognised for ibuprofen represent class risks:

- Heart failure
- Myocardial infarction (MI)
- Cerebrovascular accident (CVA)
- Gastro-intestinal bleeding, ulceration, and perforation
- Exacerbation of Ulcerative Colitis and Crohn's disease
- Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis),
- Renal toxicity/ renal failure,
- Use during third trimester of pregnancy
- Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin
- Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)
- Use by elderly
- Use by patients with (history of) bronchial asthma
- Hypersensitivity reactions
- Hypersensitivity to NSAIDs or aspirin
- Hepatic disorders
- Aseptic meningitis in patients with SLE and mixed connective tissue disease
- Premature closure of the foetal ductus arteriosus

- Impaired female fertility
- Medication Headache Overuse
- Use during 1st and 2nd trimester of pregnancy

SVII.5.2 Important pharmacological class effects not discussed above
None

Part II: Module SVIII - Summary of the safety concerns

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Heart failure - Myocardial infarction (MI) - Cerebrovascular accident (CVA) - Gastro-intestinal bleeding, ulceration, and perforation - Exacerbation of Ulcerative Colitis and Crohn's disease - Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis), - Renal toxicity/ renal failure, - Use during third trimester of pregnancy - Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin - Interaction with antihypertensive agents (e.g. diuretics, beta-blockers) - Use by elderly - Use by patients with (history of) bronchial asthma - Hypersensitivity reactions - Hypersensitivity to NSAIDs or aspirin - Hepatic disorders - Aseptic meningitis in patients with SLE and mixed connective tissue disease - Premature closure of the foetal ductus arteriosus
Important potential risks	- Impaired female fertility - Medication Overuse Headache (MOH) - Use during 1st and 2nd trimester of pregnancy - Second myocardial infarction after treatment with ibuprofen
Important missing information	- Use for > 14 days

Part III: Pharmacovigilance Plan

III.1 Safety concerns and overview of planned pharmacovigilance actions

Heart failure			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Myocardial infarction (MI)			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Age groups at special risk Mechanism	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Cerebrovascular accident (CVA)			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Gastro-intestinal bleeding, ulceration, and perforation			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this

Gastro-intestinal bleeding, ulceration, and perforation			
			safety concern and evaluate how it changes the current risk characterisation.

Exacerbation of Ulcerative Colitis and Crohn's disease			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Correlation with dose and treatment duration	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Groups of patients at increased risk	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Renal toxicity/ renal failure			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Correlation with dose and treatment duration Reversibility	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Use during third trimester of pregnancy			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives

Use during third trimester of pregnancy			
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Use by elderly			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Use by patients with (history of) bronchial asthma			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Hypersensitivity reactions			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Patients at risk Correlation with treatment and treatment duration Management Preventability	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Hypersensitivity to NSAIDs or aspirin			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Patients at risk Correlation with treatment and treatment duration Management Preventability	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Hepatic disorders			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Preventability Management Correlation with treatment and treatment duration	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it

Hepatic disorders			
			changes the current risk characterisation.

Aseptic meningitis			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Frequency Preventability	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Premature closure of the foetal ductus arteriosus			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Preventability	Routine PhV activities	None	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes the current risk characterisation.

Impaired female fertility			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Impaired female fertility is a potential risk, which must be investigated further to establish a causality relatio. Mechanism	Routine pharmacovigilance activities	None	Capture and evaluate any post marketing data related to impaired female fertility.

Medication Overuse Headache (MOH)			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Medication Over-	Routine pharmaco-	None	Capture and evalu-

Medication Overuse Headache (MOH)			
use Headache (MOH) is a potential risk, which must be investigated further to establish a causality relation.	vigilance activities		ate any post marketing data related to Medication Overuse Headache.

Use during 1st and 2nd trimester of pregnancy			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Use during 1st and 2nd trimester pregnancy is a potential risk, which must be investigated further to establish a causality relation.	Routine pharmacovigilance activities	None	Capture and evaluate any post marketing data related to use during 1st and 2nd trimester of pregnancy.

Second myocardial infarction after treatment with ibuprofen			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Second myocardial infarction after treatment with ibuprofen is a potential risk. A causal relation cannot be established until this potential risk has been investigated further.	Routine pharmacovigilance activities	None	Capture and evaluate any post marketing data related to second myocardial infarction after treatment with ibuprofen.

Use for > 14 days			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Use for more than 14 days is missing information, which must be investigated further to establish a causality relation between ibuprofen and any possible	Routine pharmacovigilance activities	None	Capture and evaluate any post marketing data related to use for > 14 days.

Use for > 14 days			
adverse reactions to long term treatment			

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

No additional Pharmacovigilance activities are in place in order to assess the effectiveness of risk minimisation measures.

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

No studies or activities aiming to investigate safety concerns or risk minimisation measures have been completed since the last update of the Pharmacovigilance Plan.

III.4 Details of outstanding additional pharmacovigilance activities

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

Actavis has no additional Pharmacovigilance activities imposed.

III.4.2 Mandatory additional PhV Activity (being a Specific Obligation)

Actavis has no mandatory additional pharmacovigilance activities, being a Specific Obligation.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

Actavis has no additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures.

III.4.4 Stated additional pharmacovigilance activities

Actavis has no additional pharmacovigilance activities that may provide additional supportive evidence for any safety concern.

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Actavis has no on-going or planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan.

III.5.2 Table of completed studies/activities from the Pharmacovigilance Plan

Actavis has no completed additional pharmacovigilance studies/activities in the Pharmacovigilance Plan.

Part IV: Plans for post-authorisation efficacy studies

IV.1 Applicability of efficacy to all patients in the target population

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population taking into account factors such as age, sex, race or organ impairment.

IV.2 Tables of post-authorisation efficacy studies

No efficacy studies have been imposed by the CHMP/NCA and/or are Specific Obligations. In addition, no post-authorisation efficacy studies are proposed by Actavis.

IV.3 Summary of Post authorisation efficacy development plan

Not applicable

IV.4 Summary of completed Post authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

Heart failure	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients regarding the risk of developing heart failure, especially in patients with a history of heart failure.
Routine risk minimisation measures	Proposed text in SPC Contraindication in section 4.3 Warning in section 4.4 regarding possible cardiovascular effects, including heart failure. Proposed text in PL Warning for the drug not to be administrate in case of heart problems. Warning that the risk of heart attack or stroke may be increased by ibuprofen. Heart failure is listed as an adverse event in section 4.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of these RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Myocardial infarction (MI)	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professional and patients in relation to the risk of myocardial infarction especially in high doses and with long-term treatment

Myocardial infarction (MI)	
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.4 and 4.8 regarding study results relating to myocardial infarction with to chronic administration of high doses of ibuprofen. Proposed text in PIL Warning regarding possible risk of heart attack when ibuprofen is taken at a high dose for a long time.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of these RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Cerebrovascular accident (CVA)	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professional and patients in relation to the risk of cerebrovascular accident especially in high doses and with long-term treatment and in patients with cerebrovascular disease.
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.4 and 4.8 regarding study results relating to stroke with high doses. Proposed text in PIL Warnings regarding possible risk of stroke when ibuprofen is taken at a high dose for a long time. Warnings regarding raised cardiovascular risk in patients with previous stroke or cardiovascular disease. Stroke is listed as a possible adverse event in section 4.

Cerebrovascular accident (CVA)	
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of these RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Gastro-intestinal bleeding, ulceration, and perforation	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients regarding the risk of developing gastro-intestinal bleeding, ulceration and perforation, especially in patients with a history of gastro-intestinal bleeding, in patients taking certain concomitant drugs, in elderly patients, and in patients on long-term high dose ibuprofen treatment. An additional objective is to ensure early drug discontinuation if signs of gastro-intestinal bleeding occur.

Gastro-intestinal bleeding, ulceration, and perforation	
Routine risk minimisation measures	Proposed text in SPC Contraindication in section 4.3 in case of a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy or in case of an active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding). Warnings in section 4.4 related to: - Category of population most affected-elderly - Caution to be exercised in patients with relevant medical history, measures to be taken regarding reducing doses or using protective agents - Cases that may be fatal and may occur without warning symptoms or without previous history of serious GI events. Ibuprofen withdrawal in case GI bleeding or ulceration occurs Text is included in section 4.5 regarding the increased risk of gastric bleeding with concomitant administration with corticosteroids, antiplatelets and other NSAIDs. Warning in section 4.8 that the most commonly observed adverse events are gastrointestinal in nature and listed adverse reactions: dyspepsia, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation, ulcers, sometimes with bleeding and perforation (see section 4.4), melaena, haematemesis, ulcerative stomatitis, colitis, exacerbation of inflammatory bowel disease, gastritis Gastro-intestinal bleeding is listed in section 4.9 as possible event in overdose. Proposed text in PL Warnings in section 2 not to administrate ibuprofen in case of stomach ulcer, perforation or bleeding, or they have had one twice or more in the past or in case perforation or a bleeding ulcer was experienced after taking a non-steroidal anti-inflammatory (NSAID) medicine. A warning is included to avoid administration of ibuprofen in patients with pre-existing conditions that may increase susceptibility to bleeding. Warning to stop the medicine in case of black tarry stools or blood-stained vomit

Gastro-intestinal bleeding, ulceration, and perforation	
	(signs of digestive tract ulcer with bleeding) appearance. Listed as possible side effects: digestive tract ulcer with or without perforation
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of these RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Exacerbation of Ulcerative Colitis and Crohn's disease	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients already suffering from Ulcerative Colitis and Crohn's disease, in relation to the risk of exacerbation of these diseases.

Exacerbation of Ulcerative Colitis and Crohn's disease	
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.4 for NSAIDs to be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated. Listed events in section 4.8: exacerbation of colitis and Crohn's disease. Proposed text PIL Warning to talk to the doctor in case the child suffers from chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis. Listed as possible side effects: worsening of inflammation of the colon (colitis) and digestive tract (Crohn's disease).
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of these RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients regarding the risk of severe skin reactions, in order to ensure early drug discontinuation.
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.4 related to: - Possible occurrence of serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. - Patients at highest risk and usual on-

Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)	
	set of reactions - Discontinuation of treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Listed reactions in section 4.8 bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. Proposed text in PIL Warning to stop the treatment in case of occurence of severe rash with blisters on the skin especially on the legs, arms, hands and feet which can also involve the face and lips (Stevens-Johnson´s syndrome). Severe allergic skin reactions are listed in section 4 as very rare adverse events.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Renal toxicity/ renal failure	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients in relation to the risk of experiencing renal toxicity/ renal failure, especially in patients already suffering from reduced renal function and the need for dose reduction in patients with renal disorders.

Renal toxicity/ renal failure	
Routine risk minimisation measures	Proposed text in SPC Contraindication in section 4.3 in severe renal insufficiency Warning in section 4.4 that renal impairment as renal function may further deteriorate, listed patients at highest risk and warning to monitor renal function, especially in high risk patients. A warning is included in section 4.5 about the possible risk of acute renal insufficiency in patients with compromised renal function where angiotensin II receptor antagonists are combined with NSAIDs. Adequate hydration and monitoring of renal function is recommended throughout the treatment. Text is included in section 4.6 regarding the risk of renal dysfunction and subsequent renal failure of the foetus upon in utero exposure to ibuprofen. Listed reaction in 4.8 : renal failure Acute renal failure is mentioned in section 4.9 in the event of overdose. Proposed text in PIL Warning not to administrate in case of severe kidney failure, or to talk to the doctor if kidney problems exist. Kidney failure listed as possible side effect.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of these RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Use during third trimester of pregnancy	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients, in order to avoid using ibuprofen in third tri-

Use during third trimester of pregnancy	
	mester of pregnancy.
Routine risk minimisation measures	Proposed text in SPC Contraindication in section 4.3 in the last trimester of pregnancy. Warning in section 4.6 related to possible effects to foetus and to the mother, if administrated in the third trimester of pregnancy, and another warning not to be administrated in the lats trimester of pregnancy. Proposed text in PIL Warning to avoid administration of ibuprofen in the last three months of pregnancy, and to address this matter to healthcare professionals before talking the medicine during pregnancy.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients of the warning of concomitant use of ibuprofen and these types of medicines that can increase the risk of bleeding and ulceration.
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.4 to avoid concomitant NSAIDs including cyclooxygenase-2 selective inhibitors and caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin or heparin, se-

Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin	
	lective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid. Listed interactions in section 4.5 with: other NSADs, anticoagulants, corticosteroids, SSRIs, anti-platelet aggregation agents. <u>Proposed text in PIL:</u> Warning to seek for healthcare professional advice if NSAIDs are coadministered with anticoagulants, antiplatelets, corticosteroids and SSRIs.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients, in order to inform of the interaction with antihypertensive agents resulting in decreased antihypertensive treatment.
Routine risk minimisation measures	<u>Proposed text in SPC</u> <u>A warning is included in section 4.4 regarding the risk of renal dysfunction with concomitant administration of antihypertensive agents.</u> Warnings are in section 4.5: • NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. • NSAIDs and diurectis may work synergistically to promote nephrotoxicity

Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)	
	• The risk of acute renal insufficiency is increased when NSAIDs are given with angiotensin II receptor antagonists The combination should be administered with caution, especially in the elderly and protective measures should be taken in all patients, including monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Adequate hydration is advised. <u>Proposed text in PIL:</u> Warning to refer to the doctor if medicines for high blood pressure (e.g. captopril, atenolol, losartan) are concomitantly taken with Ibuprofen.
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Use by elderly	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients, in order to warn about the risk of treating elderly people with ibuprofen
Routine risk minimisation measures	<u>Proposed text in SPC</u> Warning in section 4.4 that the elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Other specific warnings in this population regarding renal effects, gastrointestinal bleeding, ulceration and perforation, drug interactions with antihypertensive or diuretic agents.

Use by elderly	
	Proposed text in PIL Warning that the elderly are more likely to have some of the possible side effects listed.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Use by patients with (history of) bronchial asthma	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients, about the risk in patients with history of bronchial asthma.
Routine risk minimisation measures	Proposed text in SPC Contraindications for patients a previous history of bronchial asthma. Warning in 4.4 that bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Aggravated asthma and bronchospasm are listed as side effects in section 4.8. In section 4.9, exacerbation of asthma in asthmatics is possible in the event of overdose. Bronchodilators are recommended should this unlikely event ensue. Proposed text in PIL A contraindication is included in section 2 for patients who previously experienced asthma secondary to ibuprofen therapy. Warning in section 2 to avoid administration in asthmatics and to seek healthcare advice if ibuprofen is deemed absolutely necessary in this population.

Use by patients with (history of) bronchial asthma	
	Unexplained wheezing, worsening of existing asthma and difficulty in breathing are all side effects listed in section 4.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Hypersensitivity reactions	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals/ patients, in order ensure early diagnosis, proper management and early drug discontinuation should hypersensitivity reactions occur.

Hypersensitivity reactions	
Routine risk minimisation measures	Text in SmPC Text is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.8 as very rare adverse events secondary to ibuprofen therapy. Uticaria is listed in section 4.8 as an uncommon adverse reaction to ibuprofen. Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen. Text in PIL Section 1: Do not give this medicine to your child if: Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal inti-inflammatory drugs. Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease. Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.

Hypersensitivity reactions	
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety is-sue.
Criteria for judging the success of the proposed risk minimisation measures	Any validated signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	This will routinely be looked into, for all ADRs, as part of the signal detection process for substance name.
Results of effectiveness measurement	NA

Hypersenisitivity to NSAIDs or aspirin	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals/ patients, in order to avoid administration in patients with established hypersensitivity to NSAIDs and ensure proper management and early drug discontinuation if required in this patient group.

Hypersenisitivity to NSAIDs or aspirin	
Routine risk minimisation measures	Text in SmPC Text is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.8 as very rare adverse events secondary to ibuprofen therapy. Uticaria is listed in section 4.8 as an uncommon adverse reaction to ibuprofen. Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen. Text in PIL Section 1: Do not give this medicine to your child if: Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal inti-inflammatory drugs. Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease. Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.

Hypersenisitivity to NSAIDs or aspirin	
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety is-sue.
Criteria for judging the success of the proposed risk minimisation measures	Any validated signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	This will routinely be looked into, for all ADRs, as part of the signal detection process for substance name.
Results of effectiveness measurement	NA

Hepatic disorders	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients, in order to ensure early diagnosis, proper management and early drug discontinuation in hepatic impairment.
Routine risk minimisation measures	Text in SmPC Ibuprofen is contraindicated in section 4.3 in patients with severe hepatic insufficiency. A warning is included in section 4.4 regarding the risk of hepatic disorders associated with ibuprofen. Liver disorders are listed in section 4.8 as very rare side effects of ibuprofen. In section 4.9, liver damage is listed as a possible adverse reaction following overdose with ibuprofen. Text in PIL A contraindication is included in section 2 for patients with liver failure. A warning is included in section 2 in children with liver failure. Yellowing of the skin or eyes, pale stools or upper abdominal pain (possible signs of liver problems) are listed under section 4 as very rare adverse events.

Hepatic disorders	
Additional risk minimisation measure(s)	None applicabe
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety is-sue.
Criteria for judging the success of the proposed risk minimisation measures	Any validated signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	This will routinely be looked into, for all ADRs, as part of the signal detection process for substance name.
Results of effectiveness measurement	NA

Aseptic meningitis in patients with SLE and mixed connective tissue disease	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals/ patients, ensure early diagnosis and proper management should aseptic meningitis ensue.
Routine risk minimisation measures	Text in SmPC A warning is included in section 4.4 regarding the risk of aseptic meningitis with special focus on patients with SLE and mixed connective tissue disease. Aseptic meningitis is listed as a side effect in section 4.8. Text in PIL: Symptoms of meningitis such as stiff neck, fever, disorientation are listed as possible side effects in section 4. The text includes information on higher risk groups such as patients with pre-existing autoimmune disorders (mixed connective tissue disease and systemic lupus erythematosus).
Additional risk minimisation measure(s)	None applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety is-sue.
Criteria for judging the success of the pro-	Any validated signal identified in relation to

Aseptic meningitis in patients with SLE and mixed connective tissue disease	
posed risk minimisation measures	these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	This will routinely be looked into, for all ADRs, as part of the signal detection process for substance name.
Results of effectiveness measurement	NA

Premature closure of the foetal ductus arteriosus	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals/ patients, in order to avoid administration of ibuprofen in pregnant women and ensure early diagnosis and proper management if a diagnosis of premature closure of the foetal ductus arteriosus is made.
Routine risk minimisation measures	Text in SmPC Text is included in section 4.6 regarding use in pregnancy and possible risk of cardiotoxicity with ibuprofen including premature closure of the foetal ductus arteriosus. Text in PIL None proposed
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety is-sue.
Criteria for judging the success of the proposed risk minimisation measures	Any validated signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	This will routinely be looked into, for all ADRs, as part of the signal detection process for substance name.
Results of effectiveness measurement	NA

Impaired female fertility	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients to inform about the implication of ibuprofen administration on female fertility
Routine risk minimisation measures	Proposed text in SPC Warning in sections 4.4 and 4.6 that there is some evidence that drugs which inhibit cyclooxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is considered reversible on withdrawal of treatment. Proposed text in PIL Warning that Ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Medication Overuse Headache (MOH)	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients about Medication Overuse Headache of analgesics.
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.4 regarding possible effect of Medication headache overuse in case of long-term (>3 months) treatment with administration every two days or more frequently. The medication should be discontinued. Headache is listed as an adverse reaction of ibuprofen in section 4.8.

Medication Overuse Headache (MOH)	
	Headache is mentioned in section 4.9 in the umbrella of symptoms secondary to ibuprofen overdose. Proposed text in PIL: Headache is presented as a potential side effect of ibuprofen.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of these RMMs will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Use during 1st and 2nd trimester of pregnancy	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients in order to reduce/avoid the use of ibuprofen during 1st and 2nd trimester of pregnancy
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.6 regarding possible risk associated with the use in first and second trimester of pregnancy.The risks are believed to increase with higher doses of ibuprofen. Ibuprofen should not be given in first and second trimester pregnancy unless deemed absolutely necessary and doses should be kept as low as effectiveness allows. Proposed text PIL Warning in section 2 to seek medical advice should administration of ibuprofen be necessary in the first two trimesters of pregnancy.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is

Use during 1st and 2nd trimester of pregnancy	
	routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Second myocardial infarction after treatment with ibuprofen	
Objective(s) of the risk minimisation measures	Proposed text in SPC/PL None
Routine risk minimisation measures	None proposed.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMM and its effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

Use for > 14 days	
Objective(s) of the risk minimisation measures	Communicate currently available information to healthcare professionals and patients, on long-term (more than 14 days) use of ibuprofen.
Routine risk minimisation measures	Proposed text in SPC Warning in section 4.8 that clinical trials have shown that long term use of ibuprofen may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) . A warning is included in section 4.4 regarding the risk of medication overuse headache on long term administration of ibuprofen. Proposed text in PIL:

Use for > 14 days	
	A warning is included in section 2 concerning the risk of heart attack with high doses of ibuprofen given over a long time. The lowest amount of ibuprofen for the shortest duration is recommended in order to reduce this risk. Text is included in section 4 regarding the risk of heart attack and stroke on chronic administration of ibuprofen.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of this RMM will be evaluated by identifying disproportionate reporting of cases concerning this safety issue. This is routinely looked into, for all ADRs, as part of the signal detection process, which is performed at least yearly.
Criteria for judging the success of the proposed risk minimisation measures	Any potential signal identified in relation to these cases will be considered in the context of the proposed RMMs and their effectiveness.
Planned dates for assessment	In relation to Signal Detection
Results of effectiveness measurement	Not applicable

V.2 Risk minimisation measure failure (if applicable)

Not applicable

V.2.1 Analysis of risk minimisation measure(s) failure

Not applicable

V.2.2 Revised proposal for risk minimisation

Not applicable

V.3 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures

Heart failure	Proposed text in SPC Contraindication in section 4.3 Warning in section 4.4 regarding possible renal impairment, cardiovascular effects, including heart failure Proposed text in PL Warning for the drug not to be administrate in case of heart problems. Warning that the risk of heart attack or stroke may be increased by ibuprofen. Heart failure is listed as an adverse event in section 4.	None proposed
Myocardial infarction (MI)	Proposed text in SPC Warning in section 4.4 and 4.8 regarding study results relating to myocardial infarction with to chronic administration of high doses of ibuprofen. Proposed text in PIL Warning regarding possible risk of heart attack when ibuprofen is taken at a high dose for a long time.	None proposed
Cerebrovascular accident (CVA)	Proposed text in SPC Warning in section 4.4 and 4.8 regarding study results relating the risk of stroke on administration of high doses of ibuprofen. Proposed text in PIL Warning regarding possible risk of stroke when ibuprofen is taken at a high dose for a long time. Warnings regarding raised cardiovascular risk in patients with previous stroke or cardiovascular disease. Stroke is listed as a possible adverse event in section 4.	None proposed
Gastro-intestinal bleeding, ulceration, and perforation	Proposed text in SPC Contraindication in section 4.3 in case of a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy or in case of an active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding). Warnings in section 4.4 related to: - Category of population most affected-elderly - Caution to be exercised in patients with relevant medical history, measures to be taken regarding reducing doses or using protective agents - Cases that may be fatal and may occur	None proposed

	without warning symptoms or without previous history of serious GI events. Ibuprofen withdrawal in case GI bleeding or ulceration occurs Text is included in section 4.5 regarding the increased risk of gastric bleeding with concomitant administration with corticosteroids, antiplatelets and other NSAIDs. Warning in section 4.8 that the most commonly observed adverse events are gastrointestinal in nature and listed adverse reactions: dyspepsia, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation, ulcers, sometimes with bleeding and perforation (see section 4.4), melaena, haematemesis, ulcerative stomatitis, colitis, exacerbation of inflammatory bowel disease, gastritis. Gastro-intestinal bleeding is listed in section 4.9 as possible event in overdose. <u>Proposed text in PL</u> Warnings in section 2 not to administrate ibuprofen in case of stomach ulcer, perforation or bleeding, or they have had one twice or more in the past or in case perforation or a bleeding ulcer was experienced after taking a non-steroidal anti-inflammatory (NSAID) medicine. A warning is included to avoid administration of ibuprofen in patients with pre-existing conditions that may increase susceptibility to bleeding. Warning to stop the medicine in case of black tarry stools or blood-stained vomit (signs of digestive tract ulcer with bleeding) appearance. Listed as possible side effects: digestive tract ulcer with or without perforation	

Exacerbation of Ulcerative Colitis and Crohn's disease	Proposed text in SPC Warning in section 4.4 for NSAIDs to be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated. Listed events in section 4.8: exacerbation of colitis and Crohn's disease. Proposed text PIL Warning to talk to the doctor in case the child suffers from chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis. Listed as possible side effects: worsening of inflammation of the colon (colitis) and digestive tract (Crohn's disease).	None proposed
Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)	Proposed text in SPC Warning in section 4.4 related to: - Possible occurrence of serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. - Patients at highest risk and usual onset of reactions - Discontinuation of treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Listed reactions in section 4.8 bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. Proposed text in PIL Warning to stop the treatment in case of occurence of severe rash with blisters on the skin especially on the legs, arms, hands and feet which can also involve the face and lips (Stevens-Johnson´s syndrome). Severe allergic skin reactions are listed in section 4 as very rare adverse events.	None proposed
Renal toxicity/ renal failure	Proposed text in SPC Contraindication in section 4.3 in severe renal insufficiency Warning in section 4.4 that renal impairment as renal function may further deteriorate, listed patients at highest risk and warning to monitor renal function, especially in high risk patients. A warning is included in section 4.5 about the possible risk of acute renal	None proposed

	insufficiency in patients with compromised renal function where angiotensin II receptor antagonists are combined with NSAIDs. Adequate hydration and monitoring of renal function is recommended throughout the treatment. Text is included in section 4.6 regarding the risk of renal dysfunction and subsequent renal failure of the foetus upon in utero exposure to ibuprofen. Listed reaction in 4.8 : renal failure Acute renal failure is mentioned in section 4.9 in the event of overdose. <u>Proposed text in PIL</u> Warning not to administrate in case of severe kidney failure, or to talk to the doctor if kidney problems exist. Kidney failure listed as possible side effect.	
Use during third trimester of pregnancy	<u>Proposed text in SPC</u> Contraindication in section 4.3 in the last trimester of pregnancy. Warning in section 4.6 related to possible effects to foetus and to the mother, if administrated in the third trimester of pregnancy, and another warning not to be administrated in the lats trimester of pregnancy. <u>Proposed text in PIL</u> Warning to avoid administration of ibuprofen in the last three months of pregnancy, and to address this matter to healthcare professionals before talking the medicine during pregnancy.	None proposed
Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin	<u>Proposed text in SPC</u> Warning in section 4.4 to avoid concomitant NSAIDs including cyclooxygenase-2 selective inhibitors and caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin or heparin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid. Listed interactions in section 4.5 with: other NSADs, anticoagulants, corticosteroids, SSRIs, anti-platelet aggregation agents. <u>Proposed text in PIL:</u>	None proposed

	Warning to seek for healthcare professional advice if NSAIDs are coadministered with anticoagulants, antiplatelets, corticosteroids and SSRIs.	
Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)	Proposed text in SPC A warning is included in section 4.4 regarding the risk of renal dysfunction with concomitant administration of antihypertensive agents. Warnings are in section 4.5: • NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. • NSAIDs and diurectis may work synergistically to promote nephrotoxicity • The risk of acute renal insufficiency is increased when NSAIDs are given with angiotensin II receptor antagonists The combination should be administered with caution, especially in the elderly and protective measures should be taken in all patients, including monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Adequate hydration is advised. Proposed text in PIL: Warning to refer to the doctor if medicines for high blood pressure (e.g. captopril, atenolol, losartan) are concomitantly taken with Ibuprofen.	None proposed
Use by elderly	Proposed text in SPC Warning in section 4.4 that the elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Other specific warnings in this population regarding renal effects, gastrointestinal bleeding, ulceration and perforation, drug interactions with antihypertensive or diuretic agents. Proposed text in PIL Warning that the elderly are more likely to have some of the possible side effects listed.	None proposed

Use by patients with (history of) bronchial asthma	Proposed text in SPC Contraindications for patients a previous history of bronchial asthma. Warning in 4.4 that bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Aggravated asthma and bronchospasm are listed as side effects in section 4.8. In section 4.9, exacerbation of asthma in asthmatics is possible in the event of overdose. Bronchodilators are recommended should this unlikely event ensue. Proposed text in PIL A contraindication is included in section 2 for patients who previously experienced asthma secondary to ibuprofen therapy. Warning in section 2 to avoid administration in asthmatics and to seek healthcare advice if ibuprofen is deemed absolutely necessary in this population. Unexplained wheezing, worsening of existing asthma and difficulty in breathing are all side effects listed in section 4.	None proposed
Hypersensitivity reactions	Text in SmPC Text is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.8 as very rare adverse events secondary to ibuprofen therapy. Uticaria is listed in section 4.8 as an uncommon adverse reaction to ibuprofen.	None proposed

	Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen. <u>Text in PIL</u> Section 1: Do not give this medicine to your child if: Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal inti-inflammatory drugs. Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease. Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.	
Hypersensitivity to NSAIDs or aspirin.	<u>Text in SmPC</u> Text is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.8 as very rare adverse events	None proposed

	secondary to ibuprofen therapy. Uticaria is listed in section 4.8 as an uncommon adverse reaction to ibuprofen. Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen. <u>Text in PIL</u> Section 1: Do not give this medicine to your child if: Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal inti-inflammatory drugs. Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease. Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.	
Hepatic disorders	<u>Text in SmPC</u> Ibuprofen is contraindicated in section 4.3 in patients with severe hepatic insufficiency. A warning is included in section 4.4 regarding the risk of hepatic disorders associated with ibuprofen. Liver disorders are listed in section 4.8 as very rare side effects of ibuprofen. In section 4.9, liver damage is listed as a possible adverse reaction following overdose with ibuprofen. <u>Text in PIL</u> A contraindication is included in section 2 for patients with severe kidney, heart or liver failure. A warning is included in section 2 in chil-	None proposed

	dren with kidney, heart or liver failure. Yellowing of the skin or eyes, pale stools or upper abdominal pain (possible signs of liver problems) are listed under section 4 as very rare adverse events.	
Aseptic meningitis in patients with SLE and mixed connective tissue disease	Text in SmPC A warning is included in section 4.4 regarding the risk of aseptic meningitis with special focus on patients with SLE and mixed connective tissue disease. Aseptic meningitis is listed as a side effect in section 4.8. Text in PIL Symptoms of meningitis such as stiff neck, fever, disorientation are listed as possible side effects in section 4. The text includes information on higher risk groups such as patients with pre-existing autoimmune disorders (mixed connective tissue disease and systemic lupus erythematosus).	None proposed
Premature closure of the foetal ductus arteriosus	Text in SmPC Text is included in section 4.6 regarding use in pregnancy and possible risk of cardiotoxicity with ibuprofen including premature closure of the foetal ductus arteriosus.	None proposed
Impaired female fertility	Proposed text in SPC Warning in sections 4.4 and 4.6 that there is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility via affecting. This is considered reversible on withdrawal of treatment. Proposed text in PIL Warning that Ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine	None proposed

Medication Overuse Headache (MOH)	Proposed text in SPC Warning in section 4.4 regarding possible effect of Medication headache overuse in case of long-term (>3 months) treatment with administration every two days or more frequently. The medication should be discontinued. Headache is listed as an adverse reaction of ibuprofen in section 4.8. Headache is mentioned in section 4.9 in the umbrella of symptoms secondary to ibuprofen overdose. Proposed text in PIL: Headache is presented as a potential side effect of ibuprofen.	None proposed
Use during 1st and 2nd trimester of pregnancy Routine risk minimisation measures	Proposed text in SPC Warning in section 4.6 regarding possible risk associated with the use in first ans second trimester of pregnancy, study results, absolute risk of malformations, risk /dose dependency. Ibuprofen is not recommended in this period of pregnancy. Proposed text PIL Waning to administrate ibuprofen in the forst and second trimester of pregnancy only if advised by the doctor.	None proposed
Second myocardial infarction after treatment with ibuprofen	Proposed text in SPC/PIL None	None proposed
Use for > 14 days	Proposed text in SPC Warning in section 4.8 that clinical trials have shown that long term use of ibuprofen may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) . A warning is included in section 4.4 regarding the risk of medication overuse headache on long term administration of ibuprofen. Proposed text in PIL: A warning is included in section 2 concerning the risk of heart attack with high doses of ibuprofen given over a long time. The lowest amount of ibuprofen for the shortest duration is recommended in order to reduce this risk. Text is included in section 4 regarding the risk of heart attack and stroke on chronic	None proposed

	administration of ibuprofen.	

Part VI: Summary of the risk management plan by product

1. Ibuprofen 100 mg/5 ml oral suspension, UK/H/5608/01/DC

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	- Heart failure - Myocardial infarction (MI) - Cerebrovascular accident (CVA) - Gastro-intestinal bleeding, ulceration, and perforation - Exacerbation of Ulcerative Colitis and Crohn's disease - Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis), - Renal toxicity/ renal failure, - Use during third trimester of pregnancy - Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin - Interaction with antihypertensive agents (e.g. diuretics, beta-blockers) - Use by elderly - Use by patients with (history of) bronchial asthma - Hypersensitivity reactions - Hypersensitivity to other NSAIDs or aspirin - Hepatic disorders - Aseptic meningitis in patients with SLE and mixed connective tissue disease - Premature closure of the foetal ductus arteriosus
Important potential risks	- Impaired female fertility - Medication Overuse Headache (MOH) - Use during 1st and 2nd trimester of pregnancy - Second myocardial infarction after treatment with ibuprofen
Important missing information	- Use for > 14 days

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Actavis has no ongoing or planned studies in the Post-authorisation Pharmacovigilance Development Plan.

VI.1.3 Summary of post authorisation efficacy development plan

Actavis did not conduct any post-authorisation efficacy studies and none are planned.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Heart failure	Proposed text in SPC Contraindication in section 4.3 Warning in section 4.4 regarding possible renal impairment, cardiovascular effects, including heart failure Proposed text in PL Warning for the drug not to be administrate in case of heart problems. Warning that the risk of heart attack or stroke may be increased by ibuprofen. Heart failure is listed as an adverse event in section 4.	None proposed
Myocardial infarction (MI)	Proposed text in SPC Warning in section 4.4 and 4.8 regarding study results relating to myocardial infarction with to chronic administration of high doses of ibuprofen. Proposed text in PIL Warning regarding possible risk of heart attack when ibuprofen is taken at a high dose for a long time.	None proposed
Cerebrovascular accident (CVA)	Proposed text in SPC Warning in section 4.4 and 4.8 regarding study results relating the risk of stroke on administration of high doses of ibuprofen. Proposed text in PIL Warning regarding possible risk of stroke when ibuprofen is taken at a high dose for a long time. Warnings regarding raised cardiovascular risk in patients with previous stroke or cardiovascular disease. Stroke is listed as a possible adverse event in section 4.	None proposed

Gastro-intestinal bleeding, ulceration, and perforation	Proposed text in SPC Contraindication in section 4.3 in case of a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy or in case of an active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding). Warnings in section 4.4 related to: - Category of population most affected-elderly - Caution to be exercised in patients with relevant medical history, measures to be taken regarding reducing doses or using protective agents - Cases that may be fatal and may occur without warning symptoms or without previous history of serious GI events. Ibuprofen withdrawal in case GI bleeding or ulceration occurs Text is included in section 4.5 regarding the increased risk of gastric bleeding with concomitant administration with corticosteroids, antiplatelets and other NSAIDs. Warning in section 4.8 that the most commonly observed adverse events are gastrointestinal in nature and listed adverse reactions: dyspepsia, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation, ulcers, sometimes with bleeding and perforation (see section 4.4), melaena, haematemesis, ulcerative stomatitis, colitis, exacerbation of inflammatory bowel disease, gastritis. Gastro-intestinal bleeding is listed in section 4.9 as possible event in overdose. Proposed text in PL Warnings in section 2 not to administrate ibuprofen in case of stomach ulcer, perforation or bleeding, or they have had one twice or more in the past or in case perforation or a bleeding ulcer was experienced after taking a non-steroidal anti-inflammatory (NSAID) medicine. A warning is included to avoid administration of ibuprofen in patients with pre-existing conditions that may increase susceptibility to bleeding. Warning to stop the medicine in case of black tarry stools or blood-stained vomit	None proposed

	(signs of digestive tract ulcer with bleeding) appearance. Listed as possible side effects: digestive tract ulcer with or without perforation	
Exacerbation of Ulcerative Colitis and Crohn's disease	Proposed text in SPC Warning in section 4.4 for NSAIDs to be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated. Listed events in section 4.8: exacerbation of colitis and Crohn's disease. Proposed text PIL Warning to talk to the doctor in case the child suffers from chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis. Listed as possible side effects: worsening of inflammation of the colon (colitis) and digestive tract (Crohn's disease).	None proposed
Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)	Proposed text in SPC Warning in section 4.4 related to: - Possible occurrence of serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. - Patients at highest risk and usual onset of reactions - Discontinuation of treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Listed reactions in section 4.8 bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. Proposed text in PIL Warning to stop the treatment in case of occurence of severe rash with blisters on the skin especially on the legs, arms, hands and feet which can also involve the face and lips (Stevens-Johnson´s syndrome). Severe allergic skin reactions are listed in section 4 as very rare adverse events.	None proposed
Renal toxicity/ renal failure	Proposed text in SPC Contraindication in section 4.3 in severe renal insufficiency Warning in section 4.4 that renal impairment as renal function may further	None proposed

	deteriorate, listed patients at highest risk and warning to monitor renal function, especially in high risk patients. A warning is included in section 4.5 about the possible risk of acute renal insufficiency in patients with compromised renal function where angiotensin II receptor antagonists are combined with NSAIDs. Adequate hydration and monitoring of renal function is recommended throughout the treatment. Text is included in section 4.6 regarding the risk of renal dysfunction and subsequent renal failure of the foetus upon in utero exposure to ibuprofen. Listed reaction in 4.8 : renal failure Acute renal failure is mentioned in section 4.9 in the event of overdose. <u>Proposed text in PIL</u> Warning not to administrate in case of severe kidney failure, or to talk to the doctor if kidney problems exist. Kidney failure listed as possible side effect.	
Use during third trimester of pregnancy	<u>Proposed text in SPC</u> Contraindication in section 4.3 in the last trimester of pregnancy. Warning in section 4.6 related to possible effects to foetus and to the mother, if administrated in the third trimester of pregnancy, and another warning not to be administrated in the lats trimester of pregnancy. <u>Proposed text in PIL</u> Warning to avoid administration of ibuprofen in the last three months of pregnancy, and to address this matter to healthcare professionals before talking the medicine during pregnancy.	None proposed
Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin	<u>Proposed text in SPC</u> Warning in section 4.4 to avoid concomitant NSAIDs including cyclooxygenase-2 selective inhibitors and caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin or heparin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid.	None proposed

	Listed interactions in section 4.5 with: other NSADs, anticoagulants, corticosteroids, SSRIs, anti-platelet aggregation agents. Proposed text in PIL: Warning to seek for healthcare professional advice if NSAIDs are coadministered with anticoagulants, antiplatelets, corticosteroids and SSRIs.	
Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)	Proposed text in SPC A warning is included in section 4.4 regarding the risk of renal dysfunction with concomitant administration of antihypertensive agents. Warnings are in section 4.5: • NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. • NSAIDs and diurectis may work synergistically to promote nephrotoxicity • The risk of acute renal insufficiency is increased when NSAIDs are given with angiotensin II receptor antagonists The combination should be administered with caution, especially in the elderly and protective measures should be taken in all patients, including monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Adequate hydration is advised. Proposed text in PIL: Warning to refer to the doctor if medicines for high blood pressure (e.g. captopril, atenolol, losartan) are concomitantly taken with Ibuprofen.	None proposed
Use by elderly	Proposed text in SPC Warning in section 4.4 that the elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Other specific warnings in this population regarding renal effects, gastrointestinal bleeding, ulceration and perforation, drug interactions with antihypertensive or diuretic agents. Proposed text in PIL Warning that the elderly are more likely to have some of the possible side effects listed.	None proposed

Use by patients with (history of) bronchial asthma	Proposed text in SPC Contraindications for patients a previous history of bronchial asthma. Warning in 4.4 that bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Aggravated asthma and bronchospasm are listed as side effects in section 4.8. In section 4.9, exacerbation of asthma in asthmatics is possible in the event of overdose. Bronchodilators are recommended should this unlikely event ensue. Proposed text in PIL A contraindication is included in section 2 for patients who previously experienced asthma secondary to ibuprofen therapy. Warning in section 2 to avoid administration in asthmatics and to seek healthcare advice if ibuprofen is deemed absolutely necessary in this population. Unexplained wheezing, worsening of existing asthma and difficulty in breathing are all side effects listed in section 4.	None proposed
Hypersensitivity reactions	Text in SmPC Text is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.8 as very rare adverse events secondary to ibuprofen therapy. Uticaria is listed in section 4.8 as an uncommon adverse reaction to ibuprofen.	None proposed

	Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen. Text in PIL Section 1: Do not give this medicine to your child if: Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal inti-inflammatory drugs. Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease. Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.	
Hypersensitivity to NSAIDs or aspirin.	Text in SmPC Text is included in section 4.3 in order to avoid administration of ibuprofen in patients with known hypersensitivity to the active substance or excipients and in patients with previous episodes of hypersensitivity reactions to aspirin or other NSAIDs. A warning is included in section 4.4 to raise awareness regarding the risk of serious skin reactions (SJS, TEN, severe bullous reactions). A warning is included in section 4.4 regarding the risk of bronchospasm in patients suffering from or with a previous history of bronchial asthma or allergic disease. Severe hypersensitivity reactions (asthma, aggravated asthma, bronchospasm, facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock are listed in section 4.8 as very rare adverse events	None proposed

	secondary to ibuprofen therapy. Uticaria is listed in section 4.8 as an uncommon adverse reaction to ibuprofen. Text is included in section 4.9 regarding the risk of exacerbation of asthma upon overdosing with ibuprofen. <u>Text in PIL</u> Section 1: Do not give this medicine to your child if: Ibuprofen is not indicated in patients with known allergies to ibuprofen or any of the excipients or in patients with prior hypersensitivity reactions to aspirin or any other non-steroidal inti-inflammatory drugs. Text is included under warning and precautions to advise addressing to healthcare professionals should administration of ibuprofen be necessary in patients with asthma, history of asthma or other allergic disease. Severe allergic reactions (swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse) are listed in section 4 as very rare side effects. Allergic skin reactions such as itchy, red, raised rash are listed as uncommon events in section 4.	
Hepatic disorders	<u>Text in SmPC</u> Ibuprofen is contraindicated in section 4.3 in patients with severe hepatic insufficiency. A warning is included in section 4.4 regarding the risk of hepatic disorders associated with ibuprofen. Liver disorders are listed in section 4.8 as very rare side effects of ibuprofen. In section 4.9, liver damage is listed as a possible adverse reaction following overdose with ibuprofen. <u>Text in PIL</u> A contraindication is included in section 2 for patients with severe kidney, heart or liver failure. A warning is included in section 2 in chil-	None proposed

	dren with kidney, heart or liver failure. Yellowing of the skin or eyes, pale stools or upper abdominal pain (possible signs of liver problems) are listed under section 4 as very rare adverse events.	
Aseptic meningitis in patients with SLE and mixed connective tissue disease	Text in SmPC A warning is included in section 4.4 regarding the risk of aseptic meningitis with special focus on patients with SLE and mixed connective tissue disease. Aseptic meningitis is listed as a side effect in section 4.8. Text in PIL Symptoms of meningitis such as stiff neck, fever, disorientation are listed as possible side effects in section 4. The text includes information on higher risk groups such as patients with pre-existing autoimmune disorders (mixed connective tissue disease and systemic lupus erythematosus).	None proposed
Premature closure of the foetal ductus arteriosus	Text in SmPC Text is included in section 4.6 regarding use in pregnancy and possible risk of cardiotoxicity with ibuprofen including premature closure of the foetal ductus arteriosus.	None proposed
Impaired female fertility	Proposed text in SPC Warning in sections 4.4 and 4.6 that there is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility via affecting. This is considered reversible on withdrawal of treatment. Proposed text in PIL Warning that Ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine	None proposed

Medication Overuse Headache (MOH)	Proposed text in SPC Warning in section 4.4 regarding possible effect of Medication headache overuse in case of long-term (>3 months) treatment with administration every two days or more frequently. The medication should be discontinued. Headache is listed as an adverse reaction of ibuprofen in section 4.8. Headache is mentioned in section 4.9 in the umbrella of symptoms secondary to ibuprofen overdose. Proposed text in PIL: Headache is presented as a potential side effect of ibuprofen.	None proposed
Use during 1st and 2nd trimester of pregnancy	Proposed text in SPC Warning in section 4.6 regarding possible risk associated with the use in first ans second trimester of pregnancy, study results, absolute risk of malformations, risk /dose dependency. Ibuprofen is not recommended in this period of pregnancy. Proposed text PIL Waning to administrate ibuprofen in the forst and second trimester of pregnancy only if advised by the doctor.	None proposed
Second myocardial infarction after treatment with ibuprofen	Proposed text in SPC/PIL None	None proposed
Use for > 14 days	Proposed text in SPC Warning in section 4.8 that clinical trials have shown that long term use of ibuprofen may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) . A warning is included in section 4.4 regarding the risk of medication overuse headache on long term administration of ibuprofen. Proposed text in PIL: A warning is included in section 2 concerning the risk of heart attack with high doses of ibuprofen given over a long time. The lowest amount of ibuprofen for the shortest duration is recommended in order to reduce this risk. Text is included in section 4 regarding the risk of heart attack and stroke on chronic	None proposed

	administration of ibuprofen.	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Mild to moderate pain due to sore throat, teething pain, toothache, earache, headache, minor aches and sprains

In a study comprising several EU countries, a total of 51.8 million respondents reported pain (20.9%) or just over one in five of the population 18 years of age and over. Moderate pain was reported by 29.4 million and mild pain by 9.0 million. With respect to frequency with which they had problems with pain, options ranged from daily pain to those who experienced pain once a month or less. Pain occurrence studies have consistently shown the impact of gender with women reporting more pain than men, reporting more severe and persistent pain and reporting pain in more body regions. The occurence of pain across all pain severity categories increases with age, the results (at least for severe and moderate pain) point to the highest occurence in the 40 to 59 years of age group. [1]

In Grøholt EK et al study the total occurence of headache, abdominal pain and back pain among children 7-17 years of age was 14.9, 8.3 and 4.7%, respectively. The most common pain combination was headache and abdominal pain. Pain was most frequent among girls. The occurrence was slightly higher in low educated or low-income families compared to those of high status. Children living in low educated, low-income, worker families had approximately a 1.4-fold odds of having pain. There was a strong association between the different pain conditions and between pain and other forms of distress in the same child.[2]

Fever, including post immunisation pyrexia

As many as 20% of childhood fevers have no apparent cause. A small but significant number of these patients may have a serious bacterial infection; the risk is greatest among febrile infants and children younger than 36 months, making proper diagnosis and management important. Fever accounts for 10-20% of pediatric visits to health care providers. Patients with no easily identified source of infection have a small but significant risk of a serious bacterial infection. If not recognized and treated appropriately and promptly, this can cause morbidity or mortality.

Meningitis, pneumonia, urinary tract infection (UTI), human herpesvirus 6 (HHV-6), and bacteremia are serious sources of fever in infants and young children.

Neonates' immature immune systems place them at greater risk of general infection. Blood spread of infection is most common in this age group or in patients who are immunocompromised. For these same reasons, infants who have a localised bacterial infection have a greater risk of developing end stage infection or bacteremia (baterias in the blood). [3]

Symptoms of colds and influenza

The common cold is the most common human disease, and affects people all over the globe. Adults typically have two to five infections annually and children may have six to ten colds a year (and up to twelve colds a year for school children). Each year, children suffer about 5 such infections and adults two to three infections. One study in Norwegian children aged 4 to 5 years found that 48% experienced more than two common colds annually.

Common cold infections are mainly caused by viruses (typically rhinovirus, but also coronavirus and respiratory syncytial virus, or metapneumovirus and others). For many colds, no infecting organism can be identified. Although they cause no mortality or serious morbidity, common colds are responsible for considerable discomfort, lost work, and medical costs.

Native Americans and Inuit are more likely to be infected with colds and develop complications such as otitis media more often than Caucasians. This may be explained by issues such as poverty and overcrowding rather than by ethnicity.
The World Health Organization estimates that worldwide, annual influenza epidemics result in about 3-5 million cases of severe illness and about 250,000 to 500,000 deaths. The Centers for Disease Control and Prevention (CDC) notes that the often-cited figure of 36,000 annual flu-related deaths was derived from years when the predominant virus subtype was H3N2, which tends to be more lethal than H1N1. In patients without other disease who contract seasonal influenza, the prognosis is very good. However, some patients have a prolonged recovery time and remain weak and fatigued for weeks. Mortality from seasonal influenza is highest in infants and the elderly.

VI.2.2 Summary of treatment benefits

- Pain

Dental pain
Ibuprofen in doses ranging from 400 to 2400 mg daily for up to 1 month produced pain relief in 82% of patients with headache, tooth extraction, joint pain or neuralgia. A clinical trial comparing ibuprofen, 400, 600 and 800 mg, with aluminum ibuprofen 400 mg and placebo in patients with moderate or severe pain subsequent to third molar extraction showed no evidence of a dose-response relationship between 400 and 800 mg in terms of clinical efficacy.
The efficacy of ibuprofen, paracetamol and placebo in children, ages 6-12, showed that preoperative use of ibuprofen and paracetamol may provide an interupted analgesic effect in paediatric patients who receive adequate analgesia during mandibular primary tooth extraction. In 47 children it has been observed significant decreases in the pain and distress for both the ibuprofen alone and paracetamol/ibuprofen combination.
Adenotonsillectomy
In a study comparing the effects of lidocaine and adrenaline with ibuprofen suspension (administered before adenotonsillectomy) on post-operative analgesia and initiation of oral feeding ibuprofen suspension applied pre-incisionally and local infiltration with lidocaine proved itself equally effective for post-operative analgesia.
Musculoskeletal pain, soft tissue injuries, periarticular lesions
Three studies comparing the analgesic effect of ibuprofen to either paracetamol or codeine (alone or in combination), perfomed on children, diferent ages, showed an at least equivalent analgesic effectiveness, or ibuprofen superiority.
Regarding paediatric limb fracture, ibuprofen did not provide better analgesia than paracetamol, while on ankle sprains analgesia efficacy, the efficacy of ibuprofen four times daily treatment appeared superior to the twice daily treatment but this finding was not statistically significant.
Headache
Nine studies (4273 participants) performed in adults concluded that ibuprofen is an effective treatment for acute migraine headache, providing pain relief in about half of sufferers.
The efficacy of paracetamol and ibuprofen was evaluated in to studies in children with severe to moderate migraine, aged 4.0 to 15.8 years, 4–18 years, and proved that both treatements are effective, or ibuprofen was slightly superior.
Ibuprofen (400 mg) was significantly better than paracetamol (1000 mg) for relieving pain associated with tension-type headache; both active treatments were significantly better than placebo.
Juvenile idiopathic arthritis
A comparison of efficacy and safety of a liquid formulation of ibuprofen at a dosage of 30 to 40 mg/kg/day versus those of aspirin at a dosage of 60 to 80 mg/kg/day in 92 children (age range 2-15) with juvenile rheumatoid arthritis, showed no significant intergroup differences [27]

- Fever

Data from nine studies with 1078 children were evaluated in a review which concluded that ibuprofen at 5-10 mg/kg doses was a more effective antipyretic than paracetamol at 10-15

mg/kg doses at 2, 4 and 6 hours post treatment. Another large review (85 studies included) revealed that, for the most part, ibuprofen was more efficacious than paracetamol for the treatment of pain and fever in both pediatric and adult populations, and that these 2 drugs were equally safe.
The effect of combination treatments of paracetamol and ibuprofen on fever and comfort was reviewd in six studies and they showed limited benefit from the combined treatment until around 4 h, after which there was a statistically but only marginally clinically significant benefit. Thus, there is little evidence of any benefit or harm from the combined treatment compared with the use of each drug alone.
Different comparative studies for the efficacy of ibuprofen to paracetamol in febrile children of 6 to 36 months or 0.2 and 12 years, on dosis of either paracetamol (12.5 mg/kg per dose every 6 hours) or ibuprofen (5 mg/kg per dose every 8 hours), or ibuprofen (20 mg/kg/24 hours) with paracetamol (50 mg/kg/24 hours) revealed that alteranative treatment with paracetamol and ibuprofen was more effective than monotherapy of either drug, or that ibuprofen suspension was as effective and well tolerated as paracetamol.

- Symptoms of common cold

In four studies assessing ibuprofen efficacy in the treatment of common cold symptoms like sore throat, analgesia-related symptoms, headache, earache, muscle/joint pain and increased body temperature, this substance has been proved superior to placebo.
With respect to ibuprofen tolerance compared to aspirin and parcetamol, a study comprinsing 2815 patients showed that ibuprofen was significantly better tolerated than aspirin and had comparable tolerability with paracetamol.[27]

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Heart failure	Patients with severe heart failure must not take ibuprofen. Caution is required before starting treatment in patients with a history of heart failure since heart failure has been reported in association with anti-inflammatory (NSAID) medicines treatment.	Discussion with doctor or pharmacist is required prior to starting treatment with ibuprofen
Heart attack (Myocardial infarction (MI)	Studies show that high doses and treatment with ibuprofen over a long period of time increase the risk of heart attack. There is no increased risk for short-term and low dose treatment.	By using ibuprofen at the lowest effective dose and for as short a time as possible, this risk will be diminished.
Stroke ((Cerebrovascular accident (CVA))	Studies show that high doses and treatment with ibuprofen over a long period of time increases the risk of stroke.	By using ibuprofen at the lowest effective dose and for as short a time as possible this risk will be diminished.

Risk	What is known	Preventability
	There is no increased risk for short-term and low dose treatment.	
Stomach bleeding, ulceration, and perforation (gastrointestinal bleeding, ulceration and perforation)	Use of anti-inflammatory (NSAID) medicines like ibuprofen increases the risk of stomach bleeding, ulceration and perforation, which can cause death. NSAIDs must not be given to patients who have a stomach ulcer, perforation or bleeding, or who have had two or more in the past or who have had perforation or a bleeding ulcer after taking a non-steroidal anti-inflammatory (NSAID) medicine before. The concomitant use of ibuprofen and other NSAIDs, should be avoided.	By using ibuprofen at the lowest effective dose and for as short a time as possible this risk is diminished. If symptoms of stomach bleeding appear (e.g blood in stools) treatment must be stopped immediately.
Worsening of chronic inflammatory bowel disease (Exacerbation of Ulcerative Colitis and Crohn's disease)	Non-steroidal anti-iflammatory (NSAID) medicines may worsen chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis	Caution is advised in patients with these diseases.
Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis)	Ibuprofen may cause serious skin reactions which can cause death. Patients are at highest risk of these reactions in the early stage of therapy.	Ibuprofen should be stopped with the first appearance of skin rash, mucosal lesions or any other sign of allergy.
Kidney failure (renal failure)	Patients with severe kidney problems must not be treated with ibuprofen, since ibuprofen may cause kidney failure.	Caution is advised in patients with decreased kidney function. Discussion with doctor or pharmacist is required prior to starting treatment with ibuprofen.
Use during last 3 months of pregnancy	Non-steroidal anti-inflammatory (NSAID) medicines must not be taken by women during the last 3 months of pregnancy there is a high risk of the heart, lungs and kidney of the unborn child being affected and an increased risk of complications during labour for the mother and the child.	Avoid taking ibuprofen especially in the last 3 months of pregnancy.
Interaction with drugs that can increase the risk of bleeding and ulceration, such	Use of ibuprofen and certain anti-inflammatory drugs (corticosteroids), blood	Combination therapy with drugs that protect the stomach (e.g. misoprostol or pro-

Risk	What is known	Preventability
as anti-inflammatory drug (corticosteroids), blood thinning medicines e.g. warfarin (anticoagulants), SSRIs antidepressant drugs (selective serotonin uptake inhibitors) or anti-platelet agents such as aspirin.	thinning medicines e.g. warfarin (anticoagulants), SSRIs antidepressant drugs (selective serotonin uptake inhibitors) or anti-platelet agents such as aspirin could increase the risk of stomach ulceration or bleeding.	ton pump inhibitors) could reduce the risk. Patients should inform their doctor/pharmacist if any of these medications are currently being taken.
Interaction with antihypertensive agents (e.g. diuretics, beta-blockers)	NSAIDs may reduce the effect of drugs used for high blood pressure (e.g. diuretics, beta-blockers) and increase the risk of kidney failure when used together with certain drugs for high blood pressure (angiotensin II receptor antagonists), especially in dehydrated or elderly patients.	Caution should be advised when taking NSAIDs in combination with blood pressure medication.
Use by elderly	Elderly patients have an increased frequency of side effects to non-steroidal anti-inflammatory (NSAID) medicines especially stomach bleeding and perforation which may cause death.	These patients should start treatment on the lowest dose available. Combination therapy with drugs that protect the stomach (e.g misoprostol or proton pump inhibitors) could reduce the risk.
Use by patients with (history of) asthma (bronchial asthma)	Patients who have previously experienced asthma in response to non-steroidal anti-inflammatory drugs should not take ibuprofen, since ibuprofen may cause asthma.	Avoid use of ibuprofen in these patients.
Hypersensitivity reactions	Patients may experience allergic reactions ranging from mild to life-threatening in severity. Symptoms include rashes, urticaria, breathing difficulties, swelling of the face and tongue, fever, drowsiness, diarrhoea, sickness, worsening of asthma etc.	Treatment should be discontinued with immediate effect upon first signs and symptoms of hypersensitivity reactions. Patients should be monitored until symptoms settle.
Hypersenstivity to NSAIDs and aspirin	Patients with a known hypersensitivity to ibuprofen or any excipients included in the product or patients with a prior history of allergic reactions to other NSAIDs or aspirin should not be administered ibuprofen.	Avoid use of ibuprofen in this patient group. If administration is deemed absolutely necessary then monitor throughout treatment.
Liver disorders (Hepatic disorders)	Patients may experience liver impairment while on ibuprofen. Symptoms include	Ibuprofen therapy must be discontinued upon first sygns of liver impairment.

Risk	What is known	Preventability
	yellowing of the skin and eyeballs, nausea, vomiting, malaies, confusion, sleepiness.	
Inflammation of the meninges/ brain membranes (Aseptic meningitis in patients with SLE and mixed connective tissue disease.)	Patients diagnosed with systemic lupus erythematosus and mixed connective tissue disease are predisposed to aseptic meningitis, a disease characterised by the inflammation of the brain.	Patients with known diagonsis of systemic lupus erythematosus and mixed connective tissue disease should be carefully monitored for signs and symptoms of aseptic meningitis. These include stiff neck, fever and disorientation, difficulty breathing, rapid heart rate, heart pounding, life-threatening shock.
Harmful effects of the heart and lungs of the foetus (premature closure of the foetal ductus arteriosus)	Exposure to ibuprofen in the womb may cause deficiencies of the cardiac and respiratory system respectively.	Avoid administration in pregnant women.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Impaired ability for women to become pregnant (female infertility)	There is some evidence that drugs like ibuprofen may impair the ability for women to become pregnant. This is reversed when treatment with ibuprofen is stopped.
Headache caused be overuse of painkillers (Medication Overuse Headache (MOH))	When painkillers are used over a long period of time headaches may develop or worsen. In such cases, the use of the painkiller should be discontinued in consultation with the doctor. This is known for certain medications used to treat throbbing headache (migraine), but may also be caused by other painkillers.
Use during the first 6 months of pregnancy (1st and 2nd trimester)	Non-steroidal anti-inflammatory (NSAID) medicines are not recommended to be taken by women during the first 6 months of pregnancy because of the possible risk of abnormal development of the unborn child.
Second heart attack (myocardial infarction) after treatment with ibuprofen	Based on one article, an increased risk of a second heart attack in patients who have previously experience a heart attack is suggested, however little is still known about this risk.

Missing information

Risk	What is known
Use for > 14 days	It is known that the risk of side effects increases with the duration of treatment of ibuprofen, however information is still missing

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in

lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for ibuprofen.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 1.0	NA	Important identified risks: -Cardiovascular toxicity -Dermatologic toxicity -Gastrointestinal toxicity -Hepatic toxicity -Renal toxicity Important potential risks: -Foetotoxicity and neonatal toxicity	
Version 2.0	08-01-2014	Important Identified risks: -Heart failure -Myocardial infarction (MI) -Cerebrovascular accident (CVA) -Gastro-intestinal bleeding, ulceration, and perforation -Exacerbation of Ulcerative Colitis and Crohn's dis-ease -Severe skin reactions (including Exfoliative dermati-tis, Stevens Johnson syndrome, Toxic epidermal necrolysis), -Renal toxicity/ renal failure, -Use during third trimester of pregnancy -Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or antiplatelet agents such as aspirin -Interaction with antihypertensive agents (e.g. diuret-ics, beta-blockers) -Use by elderly -Use by patients with (history of) bronchial asthma Important potential risks: -Impaired female fertility -Medication Overuse Headache (MOH) -Use during 1st and 2nd trimester of pregnancy -Second myocardial infarction after	List of safety concerns was updated according to the Assessment Report received from the NL

Version	Date	Safety Concerns	Comment
		treatment with ibuprofen Important missing information: -Off-label use of concomitant NSAIDs -Use by children <12 years of age -Use by adolescents < 40 kg -Use for > 14 days -Lactation	
2.1	NA	Important Identified risks: -Heart failure -Myocardial infarction (MI) -Cerebrovascular accident (CVA) -Gastro-intestinal bleeding, ulceration, and perforation -Exacerbation of Ulcerative Colitis and Crohn's dis-ease -Severe skin reactions (including Exfolia-tive dermati-tis, Stevens Johnson syn-drome, Toxic epidermal necrolysis), -Renal toxicity/ renal failure, -Use during third trimester of pregnancy -Interaction with medication that can in-crease the risk of bleeding and ulcera-tion, such as corticosteroids, anticoagu-lants such as warfarin, selective seroto-nin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin -Interaction with antihypertensive agents (e.g. diuret-ics, beta-blockers) -Use by elderly -Use by patients with (history of) bron-chial asthma Important potential risks: -Impaired female fertility -Medication Overuse Headache (MOH) -Use during 1st and 2nd trimester of pregnancy -Second myocardial infarction after treatment with ibuprofen Important missing information: -Off-label use of concomitant NSAIDs -Use by children <12 years of age -Use by adolescents < 40 kg -Use for > 14 days -Lactation	RMP administrative update to include the following prod-uct : Ibu-profen100mg/5ml oral suspension UK/H/5608/01DC
Version 3.0		Important Identified risks: -Heart failure -Myocardial infarction (MI)	Five more identified risks were added as requested by the assessor.

Version	Date	Safety Concerns	Comment
		-Cerebrovascular accident (CVA) -Gastro-intestinal bleeding, ulceration, and perforation -Exacerbation of Ulcerative Colitis and Crohn's dis-ease -Severe skin reactions (including Exfolia-tive dermati-tis, Stevens Johnson syn-drome, Toxic epidermal necrolysis), -Renal toxicity/ renal failure, -Use during third trimester of pregnancy -Interaction with medication that can in-crease the risk of bleeding and ulcera-tion, such as corticosteroids, anticoagu-lants such as warfarin, selective seroto-nin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin -Interaction with antihypertensive agents (e.g. diuret-ics, beta-blockers) -Use by elderly -Use by patients with (history of) bron-chial asthma -Hypersensitivity reactions -Hypersensitivity with other NSAIDs and aspirin -Hepatc disorders -Aseptic meningitis in patients with SLE and mixed connective tissue disease -Premature closure of the foetal ductus arteriosus Important potential risks: -Impaired female fertility -Medication Overuse Headache (MOH) -Use during 1st and 2nd trimester of pregnancy -Second myocardial infarction after treatment with ibuprofen Important missing information: -Off-label use of concomitant NSAIDs -Use by children <12 years of age -Use by adolescents < 40 kg -Use for > 14 days -Lactation	

Annexes

Annex 1 – EudraVigilance Interface
NA

Annex 2 –SmPC and Package Leaflets Ibuprofen Actavis oral solution 100mg/ ml

Version 3.0, 04/2013

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

/…/ <20 mg/ ml> <100 mg/5 ml> oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is ibuprofen.
<1 ml of oral suspension contains 20 mg of ibuprofen.>
<5 ml of oral suspension contains 100 mg of ibuprofen.>

Excipients with known effect:
<1 ml of oral suspension contains 400 mg of maltitol liquid.
1 ml of oral suspension contains 1.474 mg of sodium.
1 ml of oral suspension contains 100 mg of glycerol.
1 ml of oral suspension contains 0.78 mg of potassium.>

<5 ml of oral suspension contains 2 g of maltitol liquid.
5 ml of oral suspension contains 7.370 mg of sodium.
5 ml of oral suspension contains 500 mg of glycerol.
5 ml of oral suspension contains 3.9 mg of potassium.>

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White to almost white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children 3 months to 12 years (> 5 kg):
For the fast and effective reduction of fever, including post immunisation pyrexia and the fast and effective relief of the symptoms of colds and influenza and mild to moderate pain, such as a sore throat, teething pain, toothache, earache, headache, minor aches and sprains.

4.2. Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Children over 3 months of age

For post immunisation pyrexia: One 2.5 ml dose followed by one further 2.5 ml dose 6 hours later if necessary. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.

For pain, fever and symptoms of cold and influenza: The daily dosage of /…/ oral suspension is 20-30 mg/kg bodyweight in divided doses. Using the oral dosing syringe provided this can be achieved as follows:

Infants 3 – 6 months weighing more than 5 kg: One 2.5ml dose may be taken 3 times in 24 hours.
Infants 6 - 12 months (7 – 10 kg): One 2.5 ml dose may be taken 3 to 4 times in 24 hours.
Children 1 - 3 years (10 – 15 kg): One 5 ml dose may be taken 3 times in 24 hours.
Children 4 - 6 years (15 – 20 kg): 7.5 ml may be taken 3 times in 24 hours.
Children 7 - 9 years (20 – 30 kg): 10 ml may be taken 3 times in 24 hours.
Children 10 - 12 years (30 – 40 kg): 15 ml may be taken 3 times in 24 hours.

Doses should be given approximately every 6 to 8 hours, (or with a minimum of 4 hours between each dose if required).

Infants under 3 months of age or weighing less than 5 kg should not take /…/ due to lack of data on safety and efficacy.

Duration of treatment

For short-term use only.
Children aged over 6 months: If symptoms worsen or persist for more than 3 days, consult a doctor.
Children aged under 6 months: If symptoms worsen or persist for more than 24 hours, seek medical advice.

For oral administration.
Shake well before use.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Severe hepatic or severe renal insufficiency
- Severe heart failure
- Last trimester of pregnancy (See section 4.6)
- Conditions involving an increased tendency to bleeding

4.4. Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).

As with other NSAIDs, ibuprofen may mask the signs of infection.

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory:

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Other NSAIDs:
The use of Ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

Renal:
Renal impairment as renal function may further deteriorate (See section 4.3 Contraindications and Section 4.8 Undesirable effects)
Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, those taking diuretics or ACE-inhibitors and the elderly.
There is a risk of renal impairment in dehydrated children.

Hepatic:
Hepatic dysfunction (See section 4.3 Contraindications and Section 4.8 Undesirable effects)

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200mg daily) is associated with an increased risk of myocardial infarction.

Impaired female fertility:
There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Gastrointestinal bleeding, ulceration and perforation:
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low-dose acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk. (See below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Ibuprofen in case of varicella (see section 4.8).

Other precautions:
Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

Due to the presence of maltitol liquid in the composition of /…/, patients with rare hereditary problems of fructose intolerance should not take this medicine.
Maltitol liquid may have a mild laxative effect.
Each 5 ml spoonful contains 2 g of maltitol liquid. This provides 4.6 kcal per 5 ml spoonful.

This medicinal product contains 7.37 mg of sodium in each 5 ml dose. To be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid: Unless low-dose acetylsalicylic acid (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.4).

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Ibuprofen should be used with caution in combination with:

Anti-coagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

Antihypertensives, beta-blockers and diuretics: NSAIDs may reduce the effect of antihypertensives, such as ACE inhibitors, *beta-blockers and diuretics.*
Diuretics can increase the risk of nephrotoxicity of NSAIDs.
The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Amino glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: There is evidence for potential increases in plasma levels of lithium.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity

Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that coadministration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Cholestyramine; The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown

CYP2C9 Inhibitors: Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to

100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

4.6. Fertility, pregnancy and lactation

Pregnancy:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydramniosis;

the mother and the neonate, at the end of pregnancy to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently ibuprofen is contraindicated during the last trimester of pregnancy.

Lactation:
In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

Fertility:
See section 4.4 for information regarding female fertility.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None expected at recommended doses and duration of therapy.

4.8. Undesirable effects

Assessment of adverse reactions is normally based on the following occurrence frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations
Very rare: Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of non-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for anti-infective/antibiotic therapy.

Blood and lymphatic system disorders
Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Immune system disorders
Very rare: Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).
Asthma, aggravated asthma, bronchospasm
Not known: In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (See section 4.4 Special warnings and precautions for use).

Nervous system disorders
Uncommon: Headache.
Very rare: Aseptic meningitis - single cases have been reported very rarely.

Cardiac disorders and Vascular disorders
Not known: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.
Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2400mg daily) and in long-term treatment, may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Gastrointestinal disorders
The most commonly observed adverse events are gastrointestinal in nature.
Uncommon: Abdominal pain, nausea, dyspepsia.
Rare: Diarrhoea, flatulence, constipation and vomiting.
Very rare: Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis.
Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4).

Hepatobiliary disorders
Very rare: Liver disorders.

Skin and subcutaneous tissue disorders
Uncommon: Various skin rashes with urticaria and pruritus

Very rare: Severe forms of skin reactions such as exfoliative and bullous dermatoses, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis.
Not known: In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also *"Infections and infestations"*).

Renal and urinary disorders
Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9. Overdose

In children, ingestion of more than 400 mg/kg may cause symptoms. In adults, the dose response effect is less clear cut. The half-life in overdose is 1.5 to 3 hours.

Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely, diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives. ATC code: M01AE01

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Ibuprofen has been shown to have an onset of both analgesic and antipyretic action within 30 minutes.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acidon platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hour 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. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2. Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach.

When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.

The half-life of ibuprofen is about 2 hours.
In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3. Preclinical safety data

There are no preclinical safety data of relevance to the consumer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)

Citric acid anhydrous

Maltitol liquid

Xanthan gum

Hypromellose

Glycerol

Sodium chloride

Polysorbate 80

Sodium cyclamate

Acesulfame potassium

Sucralose

Orange flavour containing:

- **Flavouring components (flavouring preparations, flavouring substances, natural flavoring substances)**
- **Alpha-tocopherol (E307)**

- Benzyl alcohol

Vanillin

Purified Water

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years
Shelf life after first opening the bottle: 6 months

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

/…/ oral suspension is supplied in an amber glass bottle containing 60 ml, 100 ml or 200 ml, or an amber PET bottle containing 100 ml. The bottle is closed with a child-resistant HDPE screw cap with a PP outer cap and a PE adaptor.

Each pack also contains an oral dosing syringe with a capacity of 5 ml and marked with dosing graduations every 0.5ml. Each syringe consists of a PP syringe body and an HDPE plunger.

6.6. Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material from it should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

/…/ <20 mg/ ml> <100 mg/5 ml> oral suspension

ibuprofen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

<1 ml of suspension contains 20 mg ibuprofen.>
<5 ml of oral suspension contains 100 mg ibuprofen.>

3. LIST OF EXCIPIENTS

Also contains maltitol liquid, sodium, glycerol and potassium.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
60 ml
100 ml
200 ml

Each pack also contains an oral syringe which should be used for accurate dosing.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Shake well before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Shelf-life after first opening the bottle: 6 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

/…/ can be used for the fast, effective relief of mild to moderate pain such as sore throat, teething pain, toothache, ear ache, headache, minor aches and sprains. It can also be used to relieve the symptoms of colds and flu and to reduce fever, including fever after vaccination at 3 months of age.

Do not give this medicine to your child if:

- they are allergic to ibuprofen or any of the other ingredients of this medicine (listed in section 6 of the package leaflet)
- they have ever had a reaction (e.g. asthma, runny nose, rash, swelling of the face, tongue, lips or throat) after taking ibuprofen, acteylsalicylic acid (aspirin) or other non-steroidal-anti-inflammatory (NSAID) medicines
- they weigh less than 5 kg or are under 3 months of age
- they are taking any other anti-inflammatory (NSAID) medicines
- they have a stomach ulcer, perforation or bleeding, or they have had one twice or more in the past

- they have had perforation or a bleeding ulcer after taking a non-steroidal anti-inflammatory (NSAID) medicine (your child may have been sick and it contained blood or dark particles that look like coffee grounds, passed blood in their stools or passed black tarry stools)
- they have severe kidney, heart or liver failure
- they have a condition which increases their tendency to bleeding

Do not give to a child under 3 months of age, unless advised to do so by your doctor.

For short-term use only.
Do not give to babies aged 3-6 months for longer than 24 hours.
Do not give to children aged 6 months or over for longer than 3 days.
Consult your doctor if symptoms worsen or persist.

<[To be completed nationally]>

16. INFORMATION IN BRAILLE

/…/ <20 mg/ ml> <100 mg/5 ml> oral suspension

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL FOR BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

/…/ <20 mg/ ml> <100 mg/5 ml> oral suspension

ibuprofen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

<1 ml of suspension contains 20 mg ibuprofen.>
<5 ml of oral suspension contains 100 mg ibuprofen.>

3. LIST OF EXCIPIENTS

Also contains maltitol liquid, sodium, glycerol and potassium.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
60 ml
100 ml
200 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Shake well before use.

Use the oral syringe provided for accurate dosing.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Shelf-life after first opening the bottle: 6 months

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

PACKAGE LEAFLET

Package leaflet: Information for the user

/…/ <20 mg/ ml> <100 mg/5 ml> oral suspension

Ibuprofen

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- The leaflet is written in terms of giving this medicine to your child, but if you are an adult who is intending to take this medicine yourself the information in this leaflet will apply to you as well.
- If your child gets any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- You must talk to a doctor if your child does not feel better or feels worse
  - after 24 hours if your child is aged under 6 months
  - after 3 days if your child is aged over 6 months

What is in this leaflet

1. What /…/ is and what it is used for

/…/ contains ibuprofen which belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) which act to relieve pain, swelling (inflammation) and reduce fever.

/…/ can be used for the fast, effective relief of mild to moderate pain such as sore throat, teething pain, toothache, ear ache, headache, minor aches and sprains. It can also be used to relieve the symptoms of colds and flu and to reduce fever, including fever after vaccination at 3 months of age.

2. What you need to know before giving /…/ to your child

This medicine is suitable for the majority of people but certain people should not use it. Talk to your doctor or pharmacist if you are at all unsure.

Do not give this medicine to your child if:
- they are allergic to ibuprofen or any of the other ingredients of this medicine (listed in section 6)
- they have ever had a reaction (e.g. asthma, runny nose, rash, swelling of the face, tongue, lips or throat) after taking ibuprofen, acteylsalicylic acid (aspirin) or other non-steroidal-anti-inflammatory (NSAID) medicines

- they weigh less than 5 kg or are under 3 months of age
- they are taking any other anti-inflammatory (NSAID) medicines, or aspirin with a daily dose above 75 mg (aspirin should not generally be given to children under 16, but doctors may occasionally prescribe it)
- they have a stomach ulcer, perforation or bleeding, or they have had one twice or more in the past
- they have had perforation or a bleeding ulcer after taking a non-steroidal anti-inflammatory (NSAID) medicine (your child may have been sick and it contained blood or dark particles that look like coffee grounds, passed blood in their stools or passed black tarry stools)
- they have severe kidney, heart or liver failure
- they have a condition which increases their tendency to bleeding

Warnings and precautions
Talk to your doctor , pharmacist or nurse before giving /…/.
This is especially important if:
- your child has asthma, a history of asthma or other allergic disease
- your child has or has had high blood pressure, heart problems or a stroke because there is a small increased risk of heart problems with ibuprofen
- your child has a condition which may put them at risk of heart problems, such as diabetes or high cholesterol
- your child has or has had kidney, liver or heart problems
- your child is dehydrated as there is a risk of kidney problems
- your child has connective tissue disorders such as SLE (Systemic Lupus Erythematosus)
- your child suffers from chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis.
- your child has chickenpox

Like other anti-inflammatory drugs, /…/ can mask signs of infection.

Other medicines and /…/
Tell your doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.
This is especially important if your child is taking:
- Other medicines containing ibuprofen or other NSAIDs, including those you can buy over the counter
- Aspirin 75 mg (to prevent heart attacks or strokes) – the protection may be reduced when taken with ibuprofen
- Diuretics ('water tablets')
- Anticoagulants (blood thinning medicines e.g. warfarin)
- Medicines for high blood pressure (e.g. captopril, atenolol, losartan)
- Cardiac glycosides (e.g. digoxin – used to treat particular heart problems)
- Lithium (for mood disorders)
- Methotrexate (for psoriasis, arthritis and types of cancer)
- Zidovudine (for HIV infection)
- Quinolone antibiotics (for infection)
- Corticosteroids (an anti-inflammatory drug)
- Ciclosporin or tacrolimus (to prevent organ rejection after transplant)
- SSRI antidepressant drugs (for depression)
- Antiplatelet drugs (e.g. dipyridamole, clopidogrel)
- Mifepristone (for termination of pregnancy)
- Medicines known as sulphonylureas such as glibenclamide (used to treat diabetes)
- Cholestyramine (used to lower cholesterol)
- Voriconazole or fluconazole (types of anti-fungal drugs)

Seek the advice of your doctor or pharmacist if any of the above apply. If you are not sure what types of medicines your child is taking, show the medicine to the doctor or pharmacist.

Other important information

Risk of heart attack or stroke: Ibuprofen may increase the risk if your child takes large amounts for a long time. The risk is small. Give the lowest amount for the shortest possible time to reduce this risk.

/…/ contains maltitol liquid and sodium
If you have been told by your doctor that your child has an intolerance to some sugars, contact your doctor before using this medicinal product.
Maltitol liquid may have a mild laxative effect.
Each 5 ml spoonful contains 2 g of maltitol liquid. This provides 4.6 kcal per 5 ml spoonful.

This medicinal product contains 7.37 mg of sodium in each 5 ml dose. To be taken into consideration by patients on a controlled sodium diet.

If you are an adult intending to take this medicine:
- All the information in this leaflet applies to you as well.
- If you are elderly you may be more likely to have some of the possible side effects listed later in the leaflet. Talk to your doctor before taking this medicine.
- If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure , diabetes or high cholesterol, or are a smoker) you should discuss your treatment with your doctor or pharmacist.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
During the first 6 months of pregnancy you should only take this product if advised to do so by your doctor.
DO NOT take /…/ if you are in the last 3 months of your pregnancy

Breast-feeding
In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

Fertility
Ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine. It is unlikely that this medicine, used occasionally, will affect your chances of becoming pregnant, however, tell your doctor before taking this medicine if you have problems becoming pregnant.

3. How to use /…/

Always give this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Always shake the bottle thoroughly before use.

Always use the syringe supplied with the pack. The syringe can be used to measure 2.5 ml or 5 ml by drawing the liquid to the correct mark on the syringe.

The recommended dose is:

Fever caused by immunisation	
Age	**Dose**
Babies and children 3 months and over weighing more than 5 kg	**One 2.5ml dose upto twice a day**
If necessary the second dose should be given 6 hours after the first dose. • Do not give more than 2 doses in a 24 hour period. • Do not give any more medicine after second 2.5 ml**.** See a doctor if fever continues. • Do not give to a child under 3 months of age, unless advised to do so by your doctor.	

Fever, Pain and Symptoms of Cold and Flu		
Age	**Weight**	**Dose**
3 months up to 6 months weighing over 5 kg	**Over 5 kg**	**One 2.5ml dose 3 times in 24 hours** Do not use for more than 24 hours
6 months up to 1 year	**7 – 10 kg**	**One 2.5ml dose 3 or 4 times in 24 hours**
1 year up to 4 years	**10 – 15 kg**	**One 5ml dose 3 times in 24 hours**
4 years up to 7 years	**15 – 20 kg**	**One 7.5ml (5ml + 2.5ml) dose 3 times in 24 hours**
7 years up to 10 years	**20 – 30 kg**	**One 10ml (5ml+5ml) dose 3 times in 24 hours**
10 years and older	**30 – 40 kg**	**One 15ml (5ml+5ml+5ml) dose 3 times in 24 hours**
• Doses should be given every 6 - 8 hours. Leave at least 4 hours between doses. • Do not give to a child under 3 months of age, unless advised to do so by your doctor. • For **Short-term use only** o Do not give to babies aged 3-6 months for longer than 24 hours.		

- Do not give to children aged 6 months or over for longer than 3 days
- Consult your doctor if symptoms worsen or persist

Give the lowest amount for the shortest possible time to relieve the symptoms.
If symptoms worsen at any time, talk to your doctor.

Do not give more than the amount recommended above.

Directions for using the syringe:
1. Shake the bottle thoroughly before use.
2. Push the syringe firmly into the plug (hole) in the neck of the bottle.
3. To fill the syringe, turn the bottle upside down. Whilst holding the syringe in place, gently pull the plunger down drawing the medicine to the correct mark (2.5 ml or 5 ml) on the syringe.
4. Turn the bottle the right way up, and then gently twist the syringe to remove from the bottle plug.
5. Place the end of the syringe into the child's mouth, normally to the side of the mouth between the gums and cheek. Press the plunger down to slowly and gently release the medicine.
6. If the table above advises you to give more than 5 ml of the medicine, repeat steps 2 to 5 to give your child the correct amount of medicine.
After use replace the cap on the top of the bottle tightly. Store all medicines out of the sight and reach of children.
Wash the syringe in warm water and allow to dry.

If you use more /…/ than you should
If you accidently give or take more /.../ than the recommended dose, contact a doctor straight away.

If you forget to use /…/
If you forget a dose, give then next dose when needed, provided that the last dose was taken at least 4 hours ago. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Medicines such as /…/ taken at a high dose for a long time may be associated with a small increased risk of heart attack (myocardial infarction) or stroke.

Water retention (oedema), high blood pressure and heart failure have been reported in association with NSAIDs.

If your child experiences any of the following serious side effects, stop giving this medicine and tell a doctor immediately:

Very rare *(affects less than 1 user in 10,000 users):*
- Passing blood in their stools or passing black tarry stools
- Vomiting blood or dark particles that look like coffee grounds

- Severe allergic reactions. Symptoms could be swelling of the face, tongue, neck or throat, difficulty breathing, fast heart rate, feeling faint or dizzy or collapse
- Unexplained wheezing (asthma), worsening of existing asthma, difficulty in breathing
- Severe allergic skin reactions which may include peeling, blistering and lesions of the skin
- Worsening of existing severe skin infections (you may notice a rash, blistering and discolouration of the skin, fever, drowsiness, diarrhoea and sickness)
- Symptoms of meningitis such as stiff neck, fever, disorientation. Patients with existing autoimmune disorders such as systemic lupus erythematosus or mixed connective tissue disease seem to be at more risk
- Swellings or ulcers of the stomach
- Kidney problems, which may lead to kidney failure (your child may pass more or less urine, have blood in the urine or cloudy urine, or feel breathless, very tired or weak, have no appetite, or have swollen ankles)

Not known *(cannot be estimated from the available data):*

- Severe skin infections and complications of the soft tissue during a chicken pox or shingles infection
- Heart failure (your child may be tired, have difficulty breathing or swollen legs)

If your child experiences any of the following side effects, stop giving this medicine and tell your doctor:

Uncommon *(affects 1 to 10 in 1,000 users):*

- Allergic skin reactions such as itchy, red, raised rash
- Unexplained stomach pain, indigestion, heartburn or nausea

Rare *(affects 1 to 10 in 10,000 users):*

- Unexplained vomiting

Very rare *(affects less than 1 user in 10,000 users):*

- Yellowing of the skin or eyes, pale stools or upper abdominal pain (these may be signs of liver problems)
- Tiredness or severe exhaustion, unusual bruising or unexplained bleeding and an increase in the number of infections that they get (e.g. sore throats, mouth ulcers, flu-like symptoms including fever). This scould be caused by changes in the blood

Other side effects which may occur are:

Uncommon *(affects 1 to 10 in 1,000 users):*

- Headache

Rare *(affects 1 to 10 in 10,000 users):*

- Diarrhoea, constipation and wind. Tell your doctor if these last for more than a few days or become troublesome

Very rare *(affects less than 1 user in 10,000 users):*

- Worsening of colitis or Crohn's disease
- Swellings or ulcers of the mouth lining

Not known *(cannot be estimated from the available data):*

- Fluid retention, which may cause swelling of the limbs
- High blood pressure
- A small increased risk of heart attack or stroke is posssible if a high dose of ibuprofen is taken for a long time. This is unlikely at the dose level given to children

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the na-

tional reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store /…/

Do not store above 25°C.
Shelf life after first opening the bottle: 6 months

Keep this medicine out of the sight and reach of children.

Shake well before use.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP.
The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What /…/ contains
- The active substance is ibuprofen.
- <1 ml of suspension contains 20 mg ibuprofen.>
- <5 ml of oral suspension contains 100 mg of ibuprofen.>
- The other ingredients are: sodium benzoate (E211), citric acid anhydrous, maltitol liquid, xanthan gum, hypromellose, glycerol, sodium chloride, polysorbate 80, sodium cyclamate, acesulfame potassium, sucralose, orange flavour (containing flavouring components (flavouring preparations, flavouring substances, natural flavoring substances), alpha-tocopherol (E307), benzyl alcohol), vanillin, purified water.

What /…/ looks like and contents of the pack
/…/ oral suspension is a white to almost white suspension.
/…/ oral suspension is supplied in an amber glass bottle containing 60 ml, 100 ml or 200 ml, or an amber plastic bottle containing 100 ml. The bottle is closed with a child-resistant plastic screw cap. Each pack also contains a plastic oral dosing syringe.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
<[To be completed nationally]>

Manufacturer
<[To be completed nationally]>

This medicinal product is authorised in the Member States of the EEA under the following names:

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

This leaflet was last revised in <{month YYYY}>.

Annex 3 - Worldwide marketing authorisation by country (including EEA)

A3.1 Licensing status in the EEA

Ibuprofen, oral suspension, 100 mg/5 ml

Current licence status	Country	Trade name	MA No Procedure No	MA date	Launch date	Date of Cancellation / Withdrawal/ Refusal/ Expiration
Ongoing	United Kingdom		UK/H/5608/01/DC			
Ongoing	Bulgaria		UK/H/5608/01/DC			
Ongoing	Cyprus		UK/H/5608/01/DC			
Ongoing	Ireland		UK/H/5608/01/DC			
Ongoing	Iceland		UK/H/5608/01/DC			
Ongoing	Norway		UK/H/5608/01/DC			
Ongoing	Poland		UK/H/5608/01/DC			
Ongoing	Romania		UK/H/5608/01/DC			
Ongoing	Sweden		UK/H/5608/01/DC			

A3.2 Licensing status in the rest of the world

NA

Annex 4 - Synopsis of on-going and completed clinical trial programme

NA

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

NA

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

NA

Annex 7 - Specific adverse event follow-up forms

NA

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

NA

Annex 9 - Newly available study reports for RMP parts III & IV

NA

Annex 10 - Details of proposed additional risk minimisation measures (if applicable)

NA

Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)
NA

Annex 12 - Other supporting data (including referenced material)

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