VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Paracetamol is indicated for the symptomatic treatment of pain of mild to moderate intensity, such as rheumatic and musculoskeletal pain, postoperative and post-partum pain, dental pain, low back pain, neuralgia, menstrual pain or headache. Paracetamol is also indicated for the treatment of febrile states. Pain is a direct or indirect consequence of several diseases. Chronic pain of moderate to severe intensity occurs in 19% of European adults, seriously affecting the quality of their social and working lives. Few cases were managed by specialists of pain and nearly half received inadequate pain management

VI.2.2 Summary of treatment benefits

Drugs used for pain management are based upon severity of pain and the World Health Organization (WHO) 3-step ladder guideline. For mild to moderate pain, the use of non-opiates is considered, such as Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (paracetamol should be the first drug to consider in the treatment of mild to moderate pain of musculoskeletal origin). The oral route is the first choice for analgesic medications. If unable to take oral medications, buccal, sublingual, rectal, and transdermal routes will be considered before intramuscular or subcutaneous.

A meta-analysis of single-dose Randomised Controlled Trials (RCTs) in postoperative pain found paracetamol was more effective than placebo, with few adverse effects. A Cochrane review of RCTs comparing paracetamol with placebo or NSAIDs in osteoarthritis (OA) has recently been updated. Paracetamol was superior to placebo in five of the seven placebo-controlled trials and had a similar safety profile. In the short-term RCTs comparing paracetamol with NSAIDs, paracetamol was less effective overall than NSAIDs in terms of pain, stiffness and physical function, but it caused fewer gastrointestinal (GI) side effects. People with more severe OA pain do better on NSAIDs but in mild OA pain, paracetamol and NSAIDs are similarly effective. The advantage of NSAIDs was relatively small, and other factors such as safety, patient preference and cost need should be taken into account when deciding on treatment options.

VI.2.3 Unknowns relating to treatment benefits

N/A

VI.2.4 Summary of safety concern

Important identified risks

Risk	What is known	Preventability
Hepatotoxicity / abnormal liver function (Patients with pre-existing liver disease, chronic alcoholism, malnutrition, dehydration, underweight adults)	In cases of paracetamol overdose there is a risk of liver injury including hepatitis, and liver failure particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving drugs classified as 'enzyme inducers'. Paracetamol overdose may be fatal. Increased levels of hepatic function tests are observed together with decreased prothrombin levels that may appear 12 to 48 hours after paracetamol overdose	Hepatobiliary symptoms and abnormal liver function due to paracetamol overdose may take several days to occur, even in severe cases. In case of paracetamol overdose, the person affected should seek immediate medical advice, even if there are no symptoms.
Immune reactions	Caution is recommended in asthmatic patients sensitive to acetylsalicylic acid, as mild bronchospastic reactions with paracetamol have been reported (cross-reaction) in these patients. Although it only occurrs in a minority of such patients, it can cause severe reactions in some cases, especially when high doses are administered.	Patients should be advised of these reactions.
Serious skin reactions	Serious cutaneous reactions with the treatment of paracetamol, have been reported.	This product is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
Interaction with anticoagulants	Concomitant use of paracetamol with agents reducing blood coagulation has been reported to increase anticoagulation effect leading to haemorrhage. Data on severity, seriousness and outcomes of risk are not	When paracetamol is used in high doses (over 2 g daily) or long term concomitantly with anticoagulants, the risk for bleeding may increase. Patients in this situation should contact his/her doctor.

Risk	What is known	Preventability
	systematically available. However, such events are potentially serious, depending upon the extent and location of the haemorrhage.	
Interaction with enzyme inducers	Concomitant intake of drugs that induce hepatic enzyme activity can lead to increased metabolism of paracetamol to the reactive metabolite resulting in increased liver toxicity of paracetamol.	Considering liver toxicity risk, patients should talk to their doctors before taking paracetamol concomitantly with enzyme inducing drugs.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Overdose (non-intentional and intentional)	There is a risk of accidental or intentional overdose when paracetamol is used. Certain patient groups are at particular risk of overdose; elderly patients, young children, persons with hepatic disease, chronic alcohol abuse, chronic malnutrition and those concurrently taking medicinal products that lead to enzyme induction. Overdose can be fatal. Concomitant use with other medications containing paracetamol will increase the risk of overdose.

VI.2.5 Summary of additional risk minimisation measures by safety concern

For each safety concern, a reference has been made to the part of the SmPC of Paracetamol Nutra Essential 500 mg tablets to address the specific safety concerns.

No additional risk minimization measures have been proposed. The MAH believes that the current contraindications, warnings and precautions of the SmPC of this medicinal product adequately inform prescribers and patients about the rest of safety concers.

VI.2.6 Planned post authorisation development plan

N/A

VI.2.7 Summary of changes to risk management plan over time

Version	Date	Changes
1.1	April 2017	- According to RMS Assessment Report included in the procedure FI/H/933/01: -Part VI updated -Harmonization of safety concerns with corresponding changes
1.2	November 2017	- According to RMS Assessment Report included in the procedure FI/H/933/01: - Change on the indication, deletion of joint pains - Part VI 2.2: The term acetoaminophen has been modified by paracetamol - Part VI 2.4 has been updated. The following risks information was changed: hepatotoxicity/ abnormal liver function (Patients with pre-existing liver disease, chronic alcoholism, malnutrition, dehydration, underweight adults); interaction with anticoagulants; interaction with enzyme inducers; Overdose (non-intentional and intentional).