VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Pain is one of the most common reasons for a patient to seek medical attention. Moderate or severe intensity pain can be acute or chronic. While acute pain is a normal sensation triggered in the nervous system to alert a possible injury, chronic pain is different. It persists for longer period of time. Pain signals keep firing in the nervous system for weeks, months or even years. There may have been an initial mishap – sprained back, serious infection, or there may be an on-going cause of pain – arthritis, cancer, ear infection, etc., but some people suffer with chronic pain in the absence of any past injury or evidence of body damage. Estimates suggest that 20% of adults suffer from pain globally and 10% are newly diagnosed with chronic pain each year. By any measure, pain is an enormous global health problem. A recent market research report indicates that more than 1.5 billion people worldwide suffer from chronic pain. It was also reported that approximately 49.7 million people in European Union reported pain by both its severity and frequency. Of these, 11.2 million reported severe pain, 29.4 million reported moderate pain and 9.0 million reported mild pain. Globally, it has been estimated that one in five adults suffers from pain and that another one in 10 adults is diagnosed with chronic pain each year. While pain affects all populations, regardless of age, sex, income, race/ethnicity or geography, it is not distributed equally across the globe. Those who experience pain can experience acute, chronic or intermittent pain, or a combination of the three.

VI.2.2 Summary of treatment benefits

The WHO advocates the use of an ‘analgesic ladder’ for relief of pain and to employ a combination of non-opioid analgesic with an opioid. The present combination of paracetamol with tramadol has an established place in the treatment of moderate to severe painful conditions. Initially, painful conditions are treated with non-opioids, e.g. paracetamol, thereafter, if the pain persists, mild opioids, e.g. codeine, and strong opioids, e.g. tramadol, are used in a stepwise manner.

The additive analgesic effect of the fixed-dose combination of tramadol hydrochloride/paracetamol 37.5 mg/325 mg has been established in various studies. It was demonstrated that a combination tablet was significantly more effective in controlling post-operative pain following hand surgery with local anaesthesia, as compared with tramadol hydrochloride 50 mg capsule alone. The combination has superior analgesic activity and has been found to be efficacious in acute post-operative dental pain, post-operative pain following bone and stomachic surgery, low back pain, migraine pain and as an add-on therapy for pain in joints related disorders like in degradation of joints (osteoarthritis) and in the autoimmune disease effecting mainly joints (rheumatoid arthritis). In addition to relieving pain, treatment with the combination tablet had a positive effect on patient's quality of life.

VI.2.3 Unknowns relating to treatment benefits

There is no information available regarding the effects of use of the drug product in children under 12 years of age. Information on effects after the use of the drug product during general anaesthesia is also not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Simultaneous use of drugs acting on brain (concomitant use of drugs acting on central nervous system)	Simultaneous use of this medicinal product with centrally acting drugs like antidepressants, alcohol, anaesthetics, medicines that affect the state of mind, tranquilisers, sleeping pills and other pain relievers such as morphine and codeine may cause acute intoxication and other symptoms like agitation, lack of muscle coordination, headaches and sweating. Simultaneous use of tramadol with alcohol leads to severe side effects like impairment of the patient's proper thinking, sound judgement and normal day-to-day skills. Tramadol/paracetamol film-coated tablets may increase the risk of side effects if taken along with medicines used for depression. Under such situations, patients may experience confusion, restlessness, fever, sweating, uncoordinated movement of limbs or eyes, uncontrollable jerking of muscles or diarrhoea.	Yes, patients should not take this medicinal drug product simultaneously with drugs acting on the brain. The patients should avoid intake of alcohol or alcohol-containing medicinal products simultaneously while taking this drug product. Also, due to the addictive potential of the drug, patients with an alcohol addiction history should not be prescribed with tramadol as they have a higher tendency of getting addicted to tramadol as well.

Risk	What is known	Preventability
Simultaneous use of drugs called monoamine oxidase inhibitors (MAO) inhibitors (Concomitant use of MAO inhibitors)	MAO inhibitors are drugs used to treat depression and they work by inhibiting the enzyme MAO. This medicinal product is not recommended to be used along with MAOIs (such as moclobemide, linezolid and methylthioninium chloride) or within 2 weeks of their withdrawal as the symptoms like diarrhoea, rapid heartbeat, sweating, trembling, confusion and even coma have been reported.	Yes, patients should not take this medicinal product simultaneously with drugs called MAO inhibitors. The drug product must not be also started for at least 14 days after discontinuation of treatment with MAO inhibitors.
Use in patients with liver impairment (Use in patients with hepatic impairment)	Inside the liver, paracetamol gets converted to a toxic compound which reacts with another compound, making this toxic compound harmless. However, in patients with liver impairment, the capacity to render the toxic compound harmless is compromised, and, thus, further worsening of the liver function may occur. In addition, tramadol is also primarily broken down by the liver. Therefore, in case of compromised liver function, both paracetamol and tramadol levels in the blood will rise, and this can increase the chances of various undesirable effects of the drug product.	Yes, caution should be exercised while using this medicine in patients with liver function disorder, especially in cases of severe liver impairment.
Use in patients with kidney impairment (Use in patients with renal insufficiency)	Tramadol is mainly removed from the body through kidneys and some portion of paracetamol is also excreted through kidneys. In case of kidney impairment, both the compounds stay in the body for a long time and can exert harmful effects.	Yes, patients with severe kidney function impairment should not use this medicinal product at all. In cases of moderate impairment, the dosing should be increased to 12 hourly intervals.
Use in patients experiencing seizures or those susceptible to developing seizures (Use in patients with epilepsy)	Caution is recommended while using the drug product in patients suffering from a CNS disorder characterised by convulsions (epilepsy), having	Yes, this medicine should not be used in patients in whom epilepsy is not controlled by treatment. In patients with epilepsy who are controlled by treatment may use

Risk	What is known	Preventability
	history of convulsions or patients who are at risk of developing epilepsy. It has been reported that tramadol can lead to development of convulsions in patients who are susceptible to seizures or who are taking some medicines that can lower the threshold of developing seizures (e.g. SSRIs, antidepressants, anaesthesia and centrally acting pain relievers)	this medicine if it is deemed necessary. To reduce the likelihood of any serious reactions, the lowest effective doses of tramadol should be prescribed and its use be avoided in patients with a history of seizure disorders.
Use in patients in whom opioid-containing medications should not be used (such as patients with opioid dependency, or in patients with injury to brain, state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory centre or the respiratory function, or with an increased intracranial pressure)	Tramadol can cause respiratory depression just like other opioid analgesics. Therefore, this medicinal product should be used with caution in patients with severe respiratory insufficiency. The risk of respiratory depression, however, can also increase as the dosage gets higher. This medicinal product is also recommended not to be used in patients who are dependent on opioids, or those with injury to brain, or those who are in shock or altered state of consciousness.	Yes, this medicine should not be used in patients with opioid dependency, or in patients with injury to brain, state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory centre or the respiratory function, or with an increased intracranial pressure. Simultaneous use of opioid derivatives, benzodiazepines and barbiturates also needs to be taken into consideration as it leads to increased risk of respiratory depression.
Addiction and drug dependence	Drug addiction refers to such a condition of the individual, where he/she continues to use drugs even though he/she knows that it is having an adverse effect on his/her health and well-being. Gradually, the individual builds up tolerance to a particular drug or drugs which leads to the need to take more and more of the drug in order to achieve the effect, a condition known as drug dependence. Those with a drug dependence problem are also likely to experience withdrawal symptoms when they stop taking the drug in question. Dependence on tramadol usually happens after the drug is taken	Yes, patients are advised not to take this medicinal product for longer than prescribed. If the patient has been taking this medicine for some time and wants to stop it, then the physician should be contacted.

Risk	What is known	Preventability
	at the maximum dose continuously for months. The risk of developing dependence is higher in patients with a history of addiction or dependence, in patients who take the drug in incorrect doses, and in patients who take the drug longer than necessary. In addition, tramadol also causes withdrawal symptoms if stopped abruptly. This medicine is also not considered to be a suitable substitute in opioid-dependent patients, as it cannot suppress morphine withdrawal symptoms.	
Effects on ability to drive and use machines	Simultaneous use of this medicinal product with alcohol and with other central nervous system depressants, such as other opioid derivatives, is not recommended because alcohol increases the sedative effect of opioid analgesics. Patient may feel dizziness or tiredness while taking this medicinal product simultaneously. The effect on alertness can make driving of vehicles and the use of machines dangerous.	Patients are advised not to drive or operate machinery while they are taking this medicine.
Overdose	Overdose of this medicinal product can lead to liver damage because of paracetamol or breathing difficulties because of tramadol. An overdose of paracetamol is of particular concern in young children. Symptoms of paracetamol over dosage in the first 24 hours include extreme paleness, nausea, vomiting, loss of appetite and stomachic pain. Liver damage may become apparent 12-48 hours after ingestion of excess amount. In severe poisoning, liver failure may progress to coma and death. Acute kidney failure may develop even in the absence of	Yes, this medicinal product should not be used in amounts more than those prescribed by the doctor. Despite of a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention, because of the risk of delayed, serious liver damage. The patient should inform the doctor or pharmacist about the other medicines that he/she is taking, and patients are advised not to take other products containing paracetamol or opiate derivatives concurrently with this drug product. Any adult or adolescent who had

Risk	What is known	Preventability
	severe liver damage. Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. Symptoms of tramadol over dosage most importantly include vomiting, circulatory collapse, consciousness disorders up to coma, convulsions and respiratory depression (slow breathing rate) up to respiratory arrest (stoppage of breathing)	ingested approximately 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested ≥150 mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Prior to starting the treatment, paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage. Test for increases in liver enzymes are usually observed at the start and are repeated every 24 hours. The patient should be made to vomit in order to empty the stomach (when the patient is conscious) by irritation or gastric lavage. Supportive measures such as maintaining the opening of the airway and maintaining cardiovascular function should be instituted; naloxone (a medicine) should be used to reverse respiratory depression; fits can be controlled with diazepam (a medicine). Administration of oral methionine or intravenous NAC which may have a beneficial effect up to at least 48 hours after the overdose may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy.

Important potential risks

Risk	What is known
Use during pregnancy and breastfeeding (Use during	Studies in human have shown that paracetamol has no harmful effects if used in recommended dosage during pregnancy. However, no information is available regarding the use of tramadol

pregnancy and lactation)	during pregnancy. In new born babies, it may cause some change in the breathing pattern but that is also not clinically relevant. Long-term treatment with this medicinal product during pregnancy may produce some withdrawal symptoms in new born babies. Therefore, this medicinal product is not recommended during pregnancy. In addition, this medicinal product is also not recommended to be used during breastfeeding. A breastfed infant could ingest some portion of the dose given to the mother. If the patient taking this medicinal product is pregnant or breastfeeding, or is palnning to become pregnant or is planning to have a baby, doctor or pharmacist advice should be taken before taking this medicine.

Important missing information

Risk	**What is known**
Use in children under 12 years of age	The effectiveness and safety of the combination of paracetamol and tramadol in children below the age of 12 years has not been established. Therefore, this medicinal product is not recommended for use in children under 12 years of age.
Use during general anaesthesia	Use of tramadol during general anaesthesia with products like enflurane and nitrous oxide had been reported to enhance intra-operative recall. No other reports have been reported for the use of this medicinal product under such circumstances. Therefore, due to absence of additional information, this medicinal product is not recommended for use during general anaesthesia.

VI.2.5 Summary of risk minimisation measures by safety concern

Routine risk minimisation is provided through the SPC and the patient information leaflet (link to the product information). No additional risk minimisation measures are planned for this product.

VI.2.6 Planned post-authorisation development plan

Not applicable.

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

This is the first risk management plan for Tramadol/Paracetamol 37.5 mg/325 mg Bristol Laboratories Film-coated Tablets.