The underlisted safety variations have been submitted by Marketing Authorization Holders (MAHs) and approved by the Food and Drugs Authority in line with the Variation Guidelines for Allopathic Medicines.These safety variations are being shared with healthcare professionals and patients.

| Safety Updates | | | | | | |
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| No. | Name of Drug | Active Ingredient(s) | Updated Section | Update | Date of Update | MAH |
| 1 | Flutiform | Fluticasone | Special warnings and precautions for use | Addition of texts under paediatric population to include "Limited data are available on the use of Flutiform inhaler in children under 5 years of age. Flutiform inhaler is NOT recommended for use in children under 5 years of age". | 23-Jan-20 | Napp Pharmaceuticals Limited |
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| 2 | Morphine | Morphine Sulphate 10 mg/ml Solution for Injection | Qualitative and Quantitative composition | Revision of texts to read "Each 1 ml of solution contains 10 mg of Morphine Sulfate. Excipients with known effect: Also contains 3.26 mg of sodium per ml and sodium metabisulphite (E223). For the full list of excipients, see section 6.1." | 21-Jan-20 | Macarthys Laboratories Ltd trading as Martindale Pharmaceuticals |
| | | | Pharmaceutical form | Addition of texts to include "A clear, colourless or almost colourless, particle free solution" | | |
| | | | Therapeutic Indication | Revision of texts that read " For the relief of severe pain" to read "Morphine is used for the symptomatic relief of severe pain; relief of dyspnoea of left ventricular failure and pulmonary oedema; pre-operative use". | | |
| | | | Posology and method of administration | Deletion of text that read "By intramuscular, subcutaneous or intravenous injection". | | |
| | | | | Revision of texts under elderly to read "Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderlyCaution". | | |
| | | | | Revision of heading from children to paediatric population | | |
| | | | | Addition of heading to include"Method of administration" | | |
| | | | | Addition of text under method of administration to include "By intramuscular, subcutaneous or intravenous injection". | | |
| | | | | Revision of texts that read "Hypersensitivity to any of the product's ingredients" to read "Hypersensitivity to the active substance or to any of the excipients listed in section 6.1" | | |
| | | | | Deletion of text that read "Chronic Obstructive Airways Disease, Asthma attack" | | |
| | | | | Revision of text to read "Phaeochromocytoma(due to the risk of pressor response to histamine release)". | | |
| | | | | Deletion of texts that read "Liver failure in children may precipitate coma" | | |
| | | | | Addition of texts to include "Acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated)". | | |
| | | | Special warnings and precautions for use | Addition of texts to include "Morphine Sulfate Solution for Injection contains sodium: This medicine contains less than 1 mmol sodium (23 mg) per ml , that is to say essentially 'sodium-free". | | |

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| 2 | Morphine | Morphine Sulphate 10 mg/ml Solution for Injection | Interactions with other medicinal Products products and other forms of interaction | Deletion of texts that read "Anxiolytics, Hypnotics and other CNS Depressants: Sedative effects may be enhanced by simultaneous use of morphine.<br><br>Ciprofloxacin: Morphine Sulfate should not be used as a premedication when ciprofloxacin is used for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.<br><br>Metoclopramide and domperidone: There may be antagonism of the gastrointestinal effects of metoclopramide and domperidone. | 21-Jan-20 | Macarthys Laboratories Ltd trading as Martindale Pharmaceuticals |
| | | | | Addition of texts to include "Anti-arrhythmics: There may be delayed absorption of mexiletine.<br><br>Antibacterials: The opioid analgesic papaveretum has been shown to reduce plasma ciprofloxacin concentration. The manufacturer of ciprofloxacin advises that premedication with opioid analgesics be avoided.<br><br>Antidepressants, anxiolytics, hypnotics:: Severe CNS excitation or depression (hypertension or hypotension) has been reported with the concurrent use of pethidine and monoamine oxidase inhibitors (MAOIs) including selegiline, moclobemide and linezolid. As it is possible that a similar interaction may occur with other opioid analgesics, morphine should be used with caution and consideration given to a reduction in dosage in patients receiving MAOIs". | | |
| | | | | Addition of texts "The sedative effects of morphine (opioid analgesics) are enhanced when used with depressants of the central nervous system such as hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.<br><br>Antipsychotics: possible enhanced sedative and hypotensive effect.<br>Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin): concurrent use may increase the risk of severe constipation.<br>Antimuscarinics: agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastrointestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive antimuscarinicanalgesic therapy". | | |
| | | | Fertility, pregnancy and lactation | Deletion of texts that read "Morphine should not be used during pregnancy or lactation as it crosses the placenta and is secreted in breast milk and can cause respiratory depression in the neonate". | | |

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| 2 | Morphine | Morphine Sulphate 10 mg/ml Solution for Injection | Fertility, pregnancy and lactation | Addition of texts to include "Pregnancy: Morphine sulfate should only be used when benefit is known to outweigh risk. As with all drugs it is not advisable to administer morphine during pregnancy. Morphine crosses the placental barrier. Administration during labour may cause respiratory depression in the new born infant and gastric stasis during labour, increasing the risk of inhalation pneumonia. Therefore, it is not advisable to administer morphine during labour. Babies born to opioid-dependent mothers may suffer withdrawal symptoms including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms including yawning, sneezing, mottling and fever.<br><br>Breast-feeding: While morphine can suppress lactation, the quantity from therapeutic doses that may reach the neonate via breast milk is probably insufficient to cause major problems of dependence or adverse effects. | 21-Jan-20 | Macarthys Laboratories Ltd trading as Martindale Pharmaceuticals |
| | | | Effects on ability to drive and use machines | Revision of texts from "May cause drowsiness, if affected patients should not drive or operate machinery" to read "Morphine causes drowsiness so patients should avoid driving or operating machinery" | | |

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| 2 | Morphine | Morphine Sulphate 10 mg/ml Solution for Injection | Undesirable effects | Revision of all undesirable effects to read as "The most serious hazard of therapy is respiratory depression (see section 4.9).<br>The commonest side-effects of morphine are: Nausea, Vomiting, Constipation, Drowsiness, Dizziness.<br>Tolerance generally develops with long term use, but not to constipation.<br><br>Other side effects include the following:<br>Anaphylaxis: Anaphylactic reactions following intravenous injection have been reported rarely.<br>Cardiovascular: Facial flushing, Bradycardia, Palpitations, Tachycardia, Orthostatic hypotension.<br>Central Nervous System: Myoclonus, Mental clouding, Confusion (with large doses), Hallucinations, Headache, Vertigo, Mood changes including dysphoria, Euphoria.<br>Gastrointestinal: Dry mouth, Biliary spasm<br>Disorders of the eye: Blurred or double vision or other changes in vision, Miosis<br>Sexual dysfunction: Long term use may lead to a reversible decrease in libido or potency.<br>Skin: Pruritus, Urticaria, Rash, Sweating, Contact dermatitis has been reported and pain and irritation may occur on injection.<br>Urinary: Difficulty with micturition, Ureteric spasm, Urinary retention, Antidiuretic effect.<br><br>Tolerance develops to the effects of opioids on the bladder.<br>The euphoric activity of morphine has led to its abuse and physical and psychological dependence may occur (see section 4.4)." | 21-Jan-20 | Macarthys Laboratories Ltd trading as Martindale Pharmaceuticals |
| | | | | Addition of texts to include "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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store". | | |
| | | | Pharmacological properties | Deletion of texts under pharmacodynamic properties that that read "Morphine is a powerful analgesic and narcotic and has central stimulant action. It depresses the thalamus, sensory cortex , respiratory and cough centres but stimulates the vomiting centre. Morphine increases the tone of involuntary muscles especially the sphincters of the gastro-intestinal tract" | | |

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| 2 | Morphine | Morphine Sulphate 10 mg/ml Solution for Injection | Pharmacological properties | Addition of text under pharmacodynamic properties to read "Pharmacotherapeutic group: Natural opium alkaloids,<br>ATC Code: N02AA<br>Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle. Morphine is a potent analgesic with competitive agonist actions at the μ- receptor, which is thought to mediate many of its other actions of respiratory depression, euphoria, inhibition of gut motility and physical dependence. It is possible that analgesia, euphoria and dependence may be due to the effects of morphine on a μ-1 receptor subtype, while respiratory depression and inhibition of gut motility may be due to actions on a μ-2 receptor subtype. Morphine is also a competitive agonist at the κ-receptor that mediates spinal analgesia, miosis and sedation. Morphine has no significant actions at the other two major opioid receptors, the δ- and the σ-receptors. Morphine directly suppresses cough by an effect on the cough centre in the medulla. Morphine also produces nausea and vomiting by directly stimulating the chemoreceptor trigger zone in the area postrema of the medulla. Morphine provokes the release of histamine". | 21-Jan-20 | Macarthys Laboratories Ltd trading as Martindale Pharmaceuticals |
| | | | | Deletion of texts under pharmacokinetic properties that read "Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs and spleen. Morphine is conjugated with glucuronic acid in the liver and gut into the active metabolites morphine-3-glucuronide and morphine-6-glucuronide. Up to 10% of a dose may be excreted through the bile into the faeces; the remainder is excreted in the kidneys.<br>It crosses the placenta and traces are found in sweat and milk. It is about 35% plasma protein bound. The plasma half life is 2 - 3 hours and about 60% of the dose is excreted in the urine after 24 hours. A small proportion of this is free morphine (higher in alkaline urine) and about 60 - 70% is conjugated. A small amount may be excreted in the bile.<br>The pharmacokinetics of morphine in children aged >1 year are similar to adults, with an elimination half-life of about 2 hours following IV administration. | | |
| | | | | Addition of texts under pharmacokinetic properties to include "Absorption: Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration. | | |

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| 2 | Morphine | Morphine Sulphate 10 mg/ml Solution for Injection | Pharmacological properties | Addition of texts under pharmacokinetic properties to include "Blood concentration: After an oral dose of 10mg as the sulfate, peak serum concentrations of free morphine of about 10ng/ml are attained in 15 to 60 minutes; after an intramuscular does of 10mg, peak serum concentrations of 70 to 80ng/ml are attained in 10 to 20 minutes; after an intravenous does of 10mg, serum concentrations of about 60ng/ml are obtained in 15 minutes falling to 30ng/ml after 30 minutes and to 10ng/ml after 3 hours; subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged. | 21-Jan-20 | Macarthys Laboratories Ltd trading as Martindale Pharmaceuticals |
| | | | | Addition of texts under pharmacokinetic properties to include "Half-life: Serum half life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half life in the period 6 hours onwards, 10 to 44 hours. Distribution: Widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen; lower concentrations appear in the brain and muscles; morphine crosses the placenta and traces are secreted in sweat and milk; protein binding, about 35% bound to albumin and to immunoglobulins at concentrations within the therapeutic range. | | |
| | | | | Addition of texts under pharmacokinetic properties to include "Biotransformation: Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides, with sulfate conjugation. N-demethylation, 0-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; Ndemethylation occurs to a greater extent after oral than parenteral administration; the 0-methylation pathway to form codeine has been challenged and codeine and norcodeine metabolites in urine may be formed from codeine impurities in the morphine sample studied. | | |
| | | | | Addition of texts under pharmacokinetic properties to include "Elimination: After an oral dose, about 60% is excreted in the urine in 24 hours, with about 3% excreted as free morphine in 48 hours; after parenteral dose, about 90% is excreted in 24 hours, with about 10% as free morphine, 65 to 70% as conjugated morphine, 1% as normorphine and 3% as normorphine glucuronide; after administration of large doses to addicts about 0.1% of a dose is excreted as norcodeine; urinary excretion of morphine appears to be pH dependent to some extent: as the urine becomes more acid more free morphine is excreted and as the urine becomes more alkaline more of the glucuronide conjugate is excreted; up to 10% of a dose may be excreted in the bile." | | |

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| 2 | Morphine | Morphine Sulphate 10 mg/ml Solution for Injection | Pharmaceutical particulars | Addition of texts under incompatibilities to include "Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities (sometimes attributed to particular formulations) have included aciclovir sodium, doxorubicin, fluorouracil, frusemide, heparin sodium, pethidine hydrochloride, promethazine hydrochloride and tetracyclines. Specialised references should be consulted for specific compatibility information. | 21-Jan-20 | Macarthys Laboratories Ltd trading as Martindale Pharmaceuticals |
| | | | | Addition of text uder special precautions for storage to include "Keep the ampoules in the outer carton in order to protect from light" | | |
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| Label Updates | | | | | | |
| No. | Name of Drug | Active Ingredient(s) | Updated Section | Update | Date of Update | MAH |
| 1 | Caelyx | Pegylated liposomal doxorubicin hydrochloride | What you need to know before you use Caelyx | Modification of text under Do not use Caelyx to read "- if you are allergic to doxorubicin hydrochloride, peanut or soya, or any of the ingredients of this medicine (listed in section 6)". | 26-Feb-20 | Janssen Cilag International NV |
| | | | | Addition of text to read "Caelyx contains soya oil and sodium<br>Caelyx contains soya oil. If you are allergic to peanut or soya, do not use this medicine.<br>Caelyx contains less than 1 mmol sodium (23 mg) per dose, that is to say 'essentially sodium-free". | | |
| | | | Possible side effects | Addition of text under very common side effects to read " general feeling of tiredness, weakness, feeling of pins and needles or pain in hands and feet". | | |
| | | | | Addition of text under common side effects to read "sleepiness, dizziness, fainting, bone pain, breast pain, abnormal muscle tension, muscle pain, leg cramps or swelling, general swelling, inflammation of the retina (the light detecting membrane of the eye), increased tear production, blurred vision, feeling of pins and needles or pain in hands and feet;<br>- inflammation of hair follicles, scaly skin, inflammation or rash, abnormal skin pigmentation (coloringcolouring), and nail disorder"; | | |

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| 1 | Caelyx | Pegylated liposomal doxorubicin hydrochloride | Possible side effects | Addition of text under common side effects to read "not enough water in the body (dehydration), severe weight loss and muscle wasting, low levels of calcium, magnesium, potassium or sodium in the blood, high levels of potassium in the blood;<br>- inflamed foodpipe, inflamed stomach lining, difficulty swallowing, dry mouth, passing wind, inflamed gums (gingivitis), change in sense of taste;<br>- inflammation of the vagina;<br>- pain when passing urine"; | 26-Feb-20 | Janssen Cilag International NV |
| | | | | Addition of text under uncommon side effects to read "- abnormal heart rhythm, heart beat feels fast or uneven (palpitations), heart failure, which makes you short of breath and may lead to swollen legs, cardiac arrest". | | |
| | | | | Addition of text to read "Rare side effects (may affect up to 1 in 1,000 people)<br>- blue colour to the skin and mucosa caused by low oxygen in the blood;<br>- patches of skin thickening". | | |
| | | | | Deletion of text under Reporting of side effects to read "If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine". | | |
| | | | How to store Caelyx | Modification of text to read "After dilution with Dextrose 5% in Water for Intravenous Infusion, the diluted CAELYX solution should be used immediately. Diluted product not for immediate use should be stored at 2°C to 8°C for no longer than 24 hours. Partially used vials should be discarded". | | |
| | | | Contents of the pack and other information | Additon of text under What Caelyx contains to read "- The other ingredients are α-(2-[1,2-distearoyl-sn-glycero(3)phosphooxy]ethylcarbamoyl)-ω-methoxypoly(oxyethylen)-40 sodium salt (MPEG-DSPE), fully hydrogenated soy phosphatidylcholine (HSPC), cholesterol, ammonium sulphate, sucrose, histidine, water for injections, hydrochloric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment). See section 2". | | |