1.3.1.1 PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

APIMEX 100 powder for concentrate for solution for infusion

APIMEX 500 powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial contains 100 mg pemetrexed and each 50 mL vial contains 500 mg pemetrexed, as pemetrexed dipotassium.

After reconstitution (see section 6.6), each vial contains 25 mg/mL of pemetrexed.

Excipients with known effect: [a]

Each APIMEX 100 mg vial contains approximately 18 mg potassium (less than 1 mmol) and each APIMEX 500 mg vial contains approximately 91,5 mg (2,34 mmol) potassium.

Contains sugar (mannitol)

- APIMEX 100 contains 106 mg mannitol per vial and APIMEX 500 contains 500 mg mannitol per vial.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A white to off-white lyophilised cake or powder having a blue or green tinge.

The reconstituted solution is a clear, colourless solution without visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APIMEX is indicated for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin.

APIMEX is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

4.2 Posology and method of administration

Posology

APIMEX should only be administered under the supervision of a medical practitioner qualified in the use of anti-cancer chemotherapy.

Malignant pleural mesothelioma:

Combination use with cisplatin:

Adults: In patients treated for malignant pleural mesothelioma, the recommended dose of APIMEX is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours

approximately 30 minutes after completion of APIMEX infusion on the first day of each 21-day cycle.

Patients should receive appropriate hydration prior to and/or after receiving cisplatin (see section 4.4). See cisplatin professional information for specific dosing advice.

Non-small cell lung cancer:

Single medicine use:

Adults: In patients treated for non-small cell lung cancer, the recommended dose of APIMEX is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Premedication regimen:

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after APIMEX administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day (see section 4.4).

To reduce toxicity, patients treated with APIMEX should also receive vitamin supplementation (see section 4.8). Patients should take oral folic acid or a multivitamin containing folic acid (350 to 1 000 µg) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of APIMEX. Dosing must continue during the full course of therapy and for 21 days after the last dose of APIMEX. Patients should also receive an intramuscular injection of vitamin B_{12} (1 000 µg) in the week preceding the first dose of APIMEX and once every three cycles thereafter.

Monitoring:

Patients receiving APIMEX should be monitored before each dose with a full blood count, including a differential white cell count (WCC) and platelet count. Periodic blood chemistry tests should be done to evaluate renal and hepatic function. The absolute neutrophil count (ANC) should be ≥ 1 500 cells/mm^3 and platelets should be ≥ 100 000 cells/mm^3 prior to the start of each cycle.

Dose adjustments:

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow enough time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables 1, 2, and 3, which are applicable for APIMEX used as monotherapy or in combination with cisplatin.

Table 1: Dose modification table for APIMEX (monotherapy or in combination) and cisplatin - haematologic toxicities	
Nadir ANC < 500/mm^3 and nadir platelets ≥ 50 000/mm^3	75 % of previous dose (both APIMEX and cisplatin)
Nadir platelets ≤ 50 000/mm^3 regardless of nadir ANC	50 % of previous dose (both APIMEX and cisplatin)

If patients develop non-haematologic toxicities ≥ Grade 3 (except for Grade 3 transaminase elevations), APIMEX should be withheld until resolution to less than or equal to the patient's pre-treatment value. Treatment should be resumed according to the guidelines in Table 2.

Table 2: Dose modification table for APIMEX (as monotherapy or in combination) and cisplatin: non-haematologic toxicities [a, b]		
	Dose of APIMEX (mg/m^2)	**Dose for cisplatin (mg/m^2)**
Any Grade 3[c] or 4 toxicities except mucositis	75 % of previous dose	75 % of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or Grade 3 or 4 diarrhoea	75 % of previous dose	75 % of previous dose
Grade 3 or 4 mucositis	50 % of previous dose	100 % of previous dose
[a] National Cancer Institute Common Toxicity Criteria (CTC) [b] Excluding neurotoxicity [c] Except Grade 3 transaminase elevation		

In the event of neurotoxicity, the recommended dose adjustment for APIMEXand cisplatin is documented in Table 3. Therapy should be discontinued in patients if Grade 3 or 4 neurotoxicity is observed.

Table 3. Dose modification table for APIMEX (as single medicine or in combination) and cisplatin: neurotoxicity		
CTC [a] Grade	**Dose of APIMEX (mg/m^2)**	**Dose for cisplatin (mg/m^2)**
0-1	100 % of previous dose	100 % of previous dose
2	100 % of previous dose	50 % of previous dose
[a] Common Toxicity Criteria (CTC)		

Treatment with APIMEX should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after two dose reductions (except Grade 3 transaminase elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly:

There is no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary.

Paediatric population:

APIMEX is not recommended for use in patients under 18 years of age, as safety and efficacy have not been established in this group of patients.

Patients with renal impairment:

(Standard Cockcroft and Gault formula or glomerular filtration rate measured Tc99m-DPTA serum clearance method): APIMEX is primarily eliminated unchanged by renal excretion. Patients with creatinine clearance of ≥ 45 mL/min require no dose adjustments other than those recommended for all patients. There are insufficient data on the use of APIMEX in patients with creatinine clearance below 45 mL/min; therefore, the use of APIMEX is not recommended (see section 4.8).

Patients with hepatic impairment:

No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and APIMEX pharmacokinetics were identified. However, patients with hepatic impairment such as bilirubin > 1,5 times the upper limit of normal and/or transaminase > 3,0 times the upper limit of normal (hepatic metastases

absent) or > 5,0 times the upper limit of normal (hepatic metastases present) have not been specifically studied.

Method of administration

APIMEX should be administered as an intravenous infusion over 10 minutes.

For precautions to be taken before handling or administering APIMEX, see section 6.6.

For instructions on reconstitution and dilution of APIMEX before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to pemetrexed or any of the ingredients of APIMEX

4.4 Special warnings and precautions for use[b]

APIMEX can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anaemia (or pancytopenia) (see section 4.8). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and pemetrexed should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1 500 cells/mm^3 and platelet count returns to ≥ 100 000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle (see section 4.2).

Less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and

infection with Grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore, all patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity (see section 4.2).

Skin reactions have been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see section 4.2).

An insufficient number of patients has been studied with creatinine clearance of below 45 ml/min. Therefore, the use of APIMEX in patients with creatinine clearance of < 45 ml/min is not recommended (see section 4.2).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and acetylsalicylic acid (> 1.3 g daily) for 2 days before, on the day of, and 2 days following APIMEX administration (see section 4.5).

In patients with mild to moderate renal insufficiency eligible for pemetrexed therapy NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.5).

Serious renal events, including acute renal failure, have been reported with pemetrexed (contained in APIMEX) alone, or in association with other chemotherapeutic medicines. Many of the patients in whom these occurred had underlying risk factors for the development of renal events

including dehydration or pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported. Most of these events resolved after pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is unknown. In patients with clinically significant third space fluid, consideration could be given to draining the effusion prior to APIMEX administration.

Due to the gastrointestinal toxicity of APIMEX given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been reported, usually when given in combination with another cytotoxic medicine. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors (see section 4.8).

Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended (see section 4.5).

APIMEX can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended.

Owing to the possibility of APIMEX treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

Women of childbearing potential must use effective contraception during treatment with pemetrexed (see section 4.6).

Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising substances.

Cases of radiation recall have been reported in patients who received radiotherapy weeks or years previously.

Excipients with known effect

APIMEX 100 mg powder for concentrate for solution for infusion contains approximately 18 mg (less than 1 mmol) potassium[c] and is essentially 'potassium free'.

APIMEX 500 mg powder for concentrate for solution for infusion contains approximately 91,5 mg (2,34 mmol) potassium. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicines and other forms of interaction

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic medicines (such as aminoglycosides, loop diuretics, platinum compounds, ciclosporin) with APIMEX could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. Creatinine clearance may need to be closely monitored if necessary.

Concomitant administration of substances that are also tubularly secreted (e.g., probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these medicines are combined with APIMEX. If necessary, creatinine clearance should be closely monitored.

In patients with normal renal function (creatinine clearance ≥ 80 ml/min), high doses of NSAIDs, such as ibuprofen > 1 600 mg/day) and aspirin at higher doses (≥ 1,3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of side effects. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin, concurrently with APIMEX to patients with normal function (creatinine clearance ≥ 80 ml/min).

In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of APIMEX with NSAIDs (e.g., ibuprofen) or aspirin at higher doses should be avoided for 2 days before, on the day of, and 2 days following APIMEX administration (see section 4.4).

In the absence of data regarding potential interaction with NSAIDs having longer half-lives such as piroxicam or rofecoxib, the concomitant administration with APIMEX in patients with mild to moderate renal insufficiency should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following APIMEX administration (see section 4.4). If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

The pharmacokinetics of APIMEX are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by APIMEX. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of APIMEX.

Pemetrexed undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes indicated that pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Interactions common to all cytotoxic medicines:

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is common. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Yellow fever vaccine: Risk of fatal generalised vaccination disease.

Live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated): Risk of systemic, possibly fatal, disease. The risk is increased in patients who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established. Animal studies have shown reproductive toxicity such as birth defects and other defects on the development of the foetus, the course of gestation and peri- and post-development. APIMEX should be avoided during pregnancy due to the potential risk to the foetus. Women should also be advised to avoid becoming pregnant while being treated with APIMEX.

Contraception in males and females

Women of childbearing potential must use effective contraception during treatment with APIMEX. Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the

treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended.

Breastfeeding

It is not known whether pemetrexed is excreted in human milk. It is therefore recommended that breastfeeding is discontinued during APIMEX therapy.

Fertility

Owing to the possibility of APIMEX treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

4.7 Effects on ability to drive and use machines

Caution should be exercised when driving or operating machines or tools, as fatigue and dizziness m ay occur (see section 4.8).

4.8 Undesirable effects

Infections and infestations	
Less frequent:	Infections, sepsis, colitis, interstitial pneumonitis, infection without neutropenia, radiation pneumonitis
Blood and lymphatic system disorders	
Frequent:	Decreased neutrophils/granulocytes, decreased leukocytes, decreased haemoglobin, decreased platelets, febrile neutropenia
Less frequent:	Pancytopenia, haemolytic anaemia

Immune system disorders	
Frequent:	Hypersensitivity reactions, anaphylactic shock
Metabolism and nutrition disorders	
Frequent:	Dehydration
Nervous system disorders	
Frequent:	Sensory neuropathy, motor neuropathy, taste disturbance
Less frequent:	Dizziness
Eye disorders	
Frequent:	Conjunctivitis
Less frequent:	Increased lacrimation
Cardiac disorders	
Less frequent:	Supraventricular dysrhythmias
Frequency not known:	Myocardial infarction
Vascular disorders	
Less frequent:	Pulmonary embolism
Frequency not known:	Cerebrovascular events (see section 4.4), peripheral ischaemia which may lead to extremity necrosis
Gastrointestinal disorders	
Frequent:	Nausea, anorexia, vomiting, diarrhoea, constipation, stomatitis/pharyngitis, mucositis, dyspepsia, abdominal pain

Less frequent:	Colitis, oesophagitis, radiation oesophagitis
Hepatobiliary disorders	
Frequent:	ALT (SGPT) elevation, AST (SGOT) elevation
Less frequent:	Hepatitis
Skin and subcutaneous tissue disorders	
Frequent:	Rash/ desquamation, alopecia, pruritus, erythema multiforme, hyperpigmentation
Less frequent:	Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4), radiation recall
Musculoskeletal and connective tissue disorders	
Frequency unknown:	Myalgia, arthralgia
Renal and urinary disorders	
Frequent:	Renal disorders (includes increased serum/blood creatinine, decreased glomerular filtration rate)
Frequency unknown:	Acute renal failure
General disorders and administration site conditions	
Frequent:	Fatigue, pain, oedema, fever

4.9 Overdose

Symptoms

Neutropenia, anaemia, thrombocytopenia and rash have been reported.

Other complications may include bone marrow suppression, infection with or without fever, diarrhoea and mucositis.

Management

Patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of leucovorin in the management of APIMEX overdosage should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A 26 Cytostatic agents

Pemetrexed is a multi-targeted anti-cancer antifolate substance that acts by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the biosynthesis of thymidine and purine nucleotides from the start. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are more potent inhibitors of TS and GARFT.

Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues.

Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged action of the medicine in malignant cells.

5.2 Pharmacokinetic properties

Distribution

Pemetrexed has a steady-state volume of distribution of 16,1 ℓ and is approximately 81 % bound to plasma proteins. Binding is not notably affected by varying degrees of renal impairment.

Metabolism

Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration.

Elimination

Pemetrexed is actively secreted by OAT3 (organic anion transporter).

Pemetrexed total systemic clearance is 91,8 ml/min and the elimination half-life from plasma is 3,5 hours in patients with normal renal function (creatinine clearance of 90 ml/min). Between-patient variability in clearance is moderate at 19,3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421), hydrochloric acid (E507) (to adjust pH), potassium hydroxide (E525) (to adjust pH).

6.2 Incompatibilities

APIMEX should only be reconstituted and diluted with 0,9 % sodium chloride injection or 5 % dextrose injection, without preservative.

APIMEX is physically incompatible with solutions containing calcium, such as lactated Ringer's injection and Ringer's injection.

Co-administration of APIMEX with other medicines and diluents has not been studied and is therefore not recommended.

6.3 Shelf life

Unopened vial:

24 months at or below 25 °C

Reconstituted and infusion solutions:

When prepared as directed, reconstituted and infusion solutions of APIMEX contain no antimicrobial preservatives. From a microbiological point of view, the product should therefore be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical in-use stability of the reconstituted solution of APIMEX in 0,9 % sodium chloride injection or 5 % dextrose injection were demonstrated for 96 hours when stored at 2 to 8 °C and at room temperature (at or below 25 °C).

6.4 Special precautions for storage

Unopened vials

Store the vial in the original container, at or below 25 °C. Do not freeze.

Storage of the reconstituted product in vials

See section 6.3.

6.5 Nature and contents of container

APIMEX 100: 10 mL clear glass, tubular lyo vial, with a 20 mm grey chlorobutyl double-vent lyo rubber stopper and a grey aluminum flip-off seal. Single vial packs.

Not all pack sizes may be marketed.

APIMEX 500: 50 mL clear glass, tubular lyo blow-back vial, with a 20 mm grey chlorobutyl double-vent lyo rubber stopper and a red aluminum flip-off seal. Single vial packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation

1. Use appropriate aseptic technique during the reconstitution and further dilution of APIMEX for intravenous infusion administration.
2. Calculate the dose and the number of APIMEX vials needed.

3. Reconstitute each APIMEX 100 vial with 4,05 mL of 0,9 % sodium chloride injection or 5 % dextrose injection, without preservative, resulting in a solution containing approximately 25 mg/ml APIMEX (see section 6.2 for incompatibilities). Slowly add the diluents to the vial and gently swirl each vial until the powder is completely dissolved. **Further dilution is required.**
4. Reconstitute each APIMEX 500 vial with 20,20 mL of 0,9 % sodium chloride injection or 5 % dextrose injection, without preservative, resulting in a solution containing approximately 25 mg/ml APIMEX. Slowly add the diluent to the vial and gently swirl each vial until the powder is completely dissolved. **Further dilution prior to infusion is required.**
5. The appropriate volume of reconstituted APIMEX solution must be further diluted to 100 mL with 0,9 % sodium chloride injection or 5 % dextrose injection, without preservative. The bag should be gently inverted to mix the solution to obtain a homogeneous solution.
6. APIMEX infusion solution must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.
7. APIMEX solution should then be administered by intravenous infusion over 10 minutes.
8. APIMEX solutions are for single use only. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

Handling

Procedures for proper handling and disposal should be observed. Care should be exercised in the handling and preparation of infusion solutions of APIMEX.

The use of gloves is recommended. If APIMEX solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If APIME Xsolutions contact the mucous membranes, flush thoroughly with water. APIMEX is not a vesicant. There is not a specific antidote for extravasation of APIMEX. Extravasation should be managed by local standard practice as with other non-vesicants.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Astral Pharma (Pty) Ltd

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George

6529

South Africa

8. REGISTRATION NUMBERS

APIMEX 100: 52/26/0122

APIMEX 500: 52/26/0123

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

24/11/2020

10. DATE OF REVISION OF TEXT

To be allocated