FINAL PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PEMETREXED SOLUTION 100 mg/4 ml ACCORD

PEMETREXED SOLUTION 500 mg/20 ml ACCORD

PEMETREXED SOLUTION 850 mg/34 ml ACCORD

PEMETREXED SOLUTION 1000 mg/40 ml ACCORD

Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 25 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

Each vial of 4 ml of solution contains 100 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

Each vial of 20 ml of solution contains 500 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

Each vial of 34 ml of solution contains 850 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

Each vial of 40 ml of solution contains 1000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

Excipient(s) with known effects:

Each ml of solution contains 8.44 mg (0.367 mmol) of sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless to pale yellow solution.

pH: 7.0 – 8.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

PEMETREXED SOLUTION 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

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

Posology

Malignant pleural mesothelioma

Combination use with cisplatin:

Adults: In patients treated for malignant pleural mesothelioma, the recommended dose of **PEMETREXED SOLUTION** 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 **PEMETREXED SOLUTION** infusion on the first day of each 21-day cycle. Patients should receive hydration consistent with local practice prior to and/or after receiving cisplatin. 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 **PEMETREXED SOLUTION** 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 **PEMETREXED SOLUTION** administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day. (See section 4.4 & 4.8).

To reduce toxicity, patients treated with **PEMETREXED SOLUTION** should also receive vitamin supplementation (see section 4.4 & 4.8). Patients must take oral folic acid or multivitamin containing folic acid (350 to 1000 µg) on a daily basis. At least 5 daily doses of folic acid must be taken during the 7 days preceding the first dose of **PEMETREXED SOLUTION**, and dosing should continue during the full course of therapy and for 21 days after the last dose of **PEMETREXED SOLUTION**. Patients must also receive an intramuscular injection of vitamin B_{12} (1000 µg) in the week preceding the first dose of **PEMETREXED SOLUTION** and every 3 cycles thereafter.

Monitoring

Patients receiving **PEMETREXED SOLUTION** should be monitored before each dose with a full blood count, including a differential and platelet count. Periodic blood chemistry tests should be collected to evaluate renal and hepatic function. Absolute Neutrophil Count (ANC) should be ≥ 1500 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 sufficient time for recovery. Upon recovery, patients may be retreated using the guidelines in Tables 1, 2 and 3, which are applicable for **PEMETREXED SOLUTION** used as a single medicine or in combination with cisplatin.

FINAL PROFESSIONAL INFORMATION

TABLE 1: DOSE MODIFICATION TABLE FOR PEMETREXED SOLUTION (AS A SINGLE MEDICINE OR IN COMBINATION) AND CISPLATIN: HAEMATOLOGIC TOXICITIES	
Nadir ANC < 500/mm^3 and nadir platelets ≥ 50 000/mm^3	75 % of previous dose (both medicines)
Nadir platelets < 50 000/mm^3 regardless of nadir ANC	50 % of previous dose (both medicines)

If patients develop non-hematologic toxicities (excluding neurotoxicity) ≥ Grade 3 (with the exception of Grade 3 transaminase elevations), **PEMETREXED SOLUTION** should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 2.

TABLE 2: DOSE MODIFICATION TABLE FOR PEMETREXED SOLUTION (AS SINGLE MEDICINE OR IN COMBINATION) AND CISPLATIN: NON-HAEMATOLOGIC TOXICITIES [a, b]		
	Dose of PEMETREXED SOLUTION (mg/m^2)	**Dose of cisplatin (mg/m^2)**
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 **PEMETREXED SOLUTION** and cisplatin is documented in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

TABLE 3 – DOSE MODIFICATION TABLE FOR PEMETREXED ACCORD SOLUTON AS A SINGLE MEDICINE OR IN COMBINATION) AND CISPLATIN: NEUROTOXICITY

CTC* Grade	Dose of PEMETREXED SOLUTION	Dose of Cisplatin (mg/m^2)
0 – 1	100 % of previous dose	100 % of previous dose
2	100 % of previous dose	50 % of previous dose

* Common Toxicity Criteria (CTC)

Treatment with **PEMETREXED SOLUTION** 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.

Special populations

Elderly: In clinical studies, there has been 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.

*Patients with renal impairment (*Standard Cockcroft and Gault formula or Glomerular Filtration Rate measured Tc99m-DPTA serum clearance method): **PEMETREXED SOLUTION** is primarily eliminated unchanged by renal excretion. In clinical studies, patients with creatinine clearance of $\geq$ 45 mL/min required no dosage adjustments other than those recommended to all patients.

FINAL PROFESSIONAL INFORMATION

There are insufficient data on the use of **PEMETREXED SOLUTION** in patients with creatinine clearance below 45 mL/min; therefore, the use of **PEMETREXED SOLUTION** is not recommended. (see section 4.5).

Patients with hepatic impairment: No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and **PEMETREXED SOLUTION** 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.

Paediatric population:

PEMETREXED SOLUTION 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.

Method of administration

PEMETREXED SOLUTION is administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

For instructions on reconstitution and dilution of **PEMETREXED SOLUTION** before administration, see section 6.6.

FINAL PROFESSIONAL INFORMATION

4.3 Contraindications

Hypersensitivity to pemetrexed or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6)

Concomitant yellow fever vaccine (see section 4.5)

FINAL PROFESSIONAL INFORMATION

4.4 Special warnings and precautions for use

Pemetrexed 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 ≥ 1500 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 pemetrexed 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 nonsteroidal 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 pemetrexed administration (see section 4.5).

FINAL PROFESSIONAL INFORMATION

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 alone or in association with other chemotherapeutic agents. 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 in post marketing setting with pemetrexed alone or with other chemotherapeutic medicines. 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 not fully defined. A phase 2 study of pemetrexed in 31 solid tumour patients with stable third space fluid demonstrated no difference in pemetrexed dose normalized plasma concentrations or clearance compared to patients without third space fluid collections. Thus, drainage of third space fluid collection prior to pemetrexed treatment should be considered, but may not be necessary.

Due to the gastrointestinal toxicity of pemetrexed 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 uncommonly reported during clinical studies with pemetrexed, usually when given in combination with

another cytotoxic agent. 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 4.3 and 4.5).

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. Owing to the possibility of pemetrexed 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 agents.
Cases of radiation recall have been reported in patients who received radiotherapy weeks or years previously.

This medicine contains 900 mg of sodium per maximum daily 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

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (eg. aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

FINAL PROFESSIONAL INFORMATION

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

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), high doses of non-steroidal anti-inflammatory medicines (NSAIDs, such as ibuprofen > 1600 mg/day) and acetylsalicylic acid at higher dose (≥ 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or acetylsalicylic acid, concurrently with pemetrexed 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 pemetrexed with NSAIDs (eg. ibuprofen) or acetylsalicylic acid at higher dose should be avoided for 2 days before, on the day of, and 2 days following pemetrexed 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 pemetrexed 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 pemetrexed administration (see section 4.4).
If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

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 medicines metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

FINAL PROFESSIONAL INFORMATION

Interactions common to all cytotoxics

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

Concomitant use contraindicated:

Yellow fever vaccine: risk of fatal generalised vaccinale disease (see section 4.3).

Concomitant use not recommended:

Live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated): risk of systemic, possibly fatal, disease. The risk is increased in subjects 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

Contraception in males and females

Women of childbearing potential must use effective contraception during treatment with pemetrexed. 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.

Pregnancy

There are no data from the use of pemetrexed in pregnant women but pemetrexed, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy. Animal studies have shown reproductive toxicity (see section 5.3). Pemetrexed should be avoided during pregnancy due to the potential hazard to the foetus. Women should be advised to avoid becoming pregnant when being treated with **PEMETREXED SOLUTION.**

Breast-feeding

It is not known whether pemetrexed is excreted in human milk and adverse reactions on the suckling child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy (see section 4.3).

Fertility

Owing to the possibility of pemetrexed 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

No studies on the effects on the ability to drive and use machines have been performed.

However, it has been reported that pemetrexed may cause fatigue. Therefore, patients should be cautioned against driving or operating machines if this event occurs.

FINAL PROFESSIONAL INFORMATION

4.8 Undesirable effects

Summary of safety profile

The frequently reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, leukopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. Other undesirable effects include renal toxicities, increased aminotransferases, alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy. Rarely seen events include Stevens-Johnson syndrome and Toxic epidermal necrolysis.

Tabulated list of adverse reactions

The table below provides the frequency and severity of undesirable effects that have been reported in > 5 % of 168 patients with mesothelioma who were randomised to receive cisplatin and pemetrexed and 163 patients with mesothelioma randomised to receive single medicine cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

System Organ Class	Frequency	Event*
Blood and lymphatic system disorders	Frequent	Neutrophils/granulocytes decreased; leukocytes decreased, haemoglobin decreased, platelets decreased
Metabolism and nutrition disorders	Frequent	Dehydration
Nervous system disorders	Frequent	Neuropathy - Sensory, taste disturbance
Eye disorders	Frequent	Conjunctivitis
Gastro-intestinal	Frequent	Diarrhoea, vomiting, Stomatitis/ Pharyngitis, nausea, anorexia, constipation, dyspepsia

Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia
Renal and urinary disorders	Frequent	Creatinine elevation, creatinine clearance decreased**
General disorders and administration site conditions	Frequent	Fatigue

***Refer to National Cancer Institute CTC version 2 for each grade of toxicity except the term "creatine clearance decreased."**

****Which is derived from the term "renal/genitourinary other".**

*****According to National Cancer Institute CTC (v2.0; NCL 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.**

For the purpose of this table a cut off of 5 % was used for inclusion in of all events where the reporter considered a possible relationship to pemetrexed and cisplatin. Clinically relevant CTC toxicities that were reported in ≥ 1 % and ≤ 5 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include: renal failure, infection, pyrexia, febrile neutropenia, increased AST, ALT, and GGT, urticaria and chest pain. Clinically relevant CTC toxicities that were reported in < 1 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.
The table below provides the frequency and severity of undesirable effects that have been reported in > 5 % of 265 patients randomly assigned to receive single agent pemetrexed with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single agent docetaxel. All patients were diagnosed with locally advanced or metastatic non-small cell lung cancer and received prior chemotherapy.

System Organ Class	**Frequency**	**Event***

Blood and lymphatic system disorders	Frequent	Neutrophils/granulocytes decreased, leukocytes decreased, haemoglobin decreased, platelets decreased
Gastro-intestinal	Frequent	Diarrhoea, vomiting, stomatitis/pharyngitis, nausea, anorexia, constipation
Hepatobiliary disorders	Frequent	SGPT (ALT) elevation, SGOT (AST) elevation
Skin and subcutaneous tissue disorders	Frequent	Rash/ desquamation, pruritus, alopecia
General disorders and administration site conditions	Frequent	Fatigue, fever

***Refer to National Cancer Institute CTC version 2 for each grade of toxicity.**

***According to National Cancer Institute CTC (v2.0; NCI 1998), alopecia should only be reported as Grade 1 or 2. For the purpose of this table a cut off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.**

Clinically relevant CTC toxicities that were reported in ≥ 1 % and ≤ 5 % of the patients that were randomly assigned to pemetrexed include: infection without neutropenia, febrile neutropenia, allergic reaction/hypersensitivity, increased creatinine, motor neuropathy, sensory neuropathy, erythema multiforme, and abdominal pain.

Clinically relevant CTC toxicities that were reported in < 1 % of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

FINAL PROFESSIONAL INFORMATION

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent pemetrexed studies (n = 164) and the Phase 3 single agent pemetrexed study described above, with the exception of neutropenia (12.8 % versus 5.3 %, respectively) and alanine aminotransferase elevation (15.2 % versus 1.9 %, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included both chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests**.**

The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 839 patients with NSCLC who were randomised to receive cisplatin and pemetrexed and 830 patients with NSCLC who were randomised to receive cisplatin and gemcitabine. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B_{12}.

System Organ Class	Frequency	Event*
Blood and lymphatic system disorders	Frequent	Haemoglobin decreased, neutrophils/granulocytes decreased, leukocytes decreased, platelets decreased
Nervous system disorders	Frequent	Neuropathy-sensory, taste disturbance
Gastrointestinal disorders	Frequent	Nausea, vomiting, anorexia, constipation, stomatitis/pharyngitis, diarrhoea without colostomy, dyspepsia/heartburn
Skin and subcutaneous tissue disorders	Frequent	Alopecia, rash/desquamation
Renal and urinary disorders	Frequent	Creatinine elevation

General disorders and administration site conditions	Frequent	Fatigue

***P-values <0.05 comparing pemetrexed/cisplatin to gemcitabine/cisplatin, using Fisher Exact test.**

****Refer to National Cancer Institute CTC (v2.0; NCI 1998) for each Grade of Toxicity.**

*****According to National Cancer Institute CTC (v2.0; NCI 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.**

For the purpose of this table, a cut-off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant toxicity that was reported in ≥ 1 % and ≤ 5 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include: AST increase, ALT increase, infection, febrile neutropenia, renal failure, pyrexia, dehydration, conjunctivitis, and creatinine clearance decrease.

Clinically relevant toxicity that was reported in < 1 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include: GGT increase, chest pain, arrhythmia, and motor neuropathy.
Clinically relevant toxicities with respect to gender were similar to the overall population in patients receiving pemetrexed plus cisplatin.

Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident and transient ischaemic attack have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

Rare cases of hepatitis, potentially serious, have been reported during clinical studies with pemetrexed.
Pancytopenia has been uncommonly reported during clinical trials with pemetrexed.

FINAL PROFESSIONAL INFORMATION

In clinical trials, cases of colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) have been reported uncommonly in patients treated with pemetrexed.

In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fata, have been reported uncommonly in patients treated with pemetrexed.

Uncommon cases of oedema have been reported in patients treated with pemetrexed.

Oesophagitis/radiation oesophagitis has been uncommonly reported during clinical trials with pemetrexed.

Sepsis, sometimes fatal, has been commonly reported during clinical trials with pemetrexed.

During post marketing surveillance, the following adverse reactions have been reported in patients treated with pemetrexed:

Hyperpigmentation has been commonly reported.

Uncommon cases of acute renal failure have been reported with pemetrexed alone or in association with other chemotherapeutic agents (see section 4.4).

Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post marketing setting with an unknown frequency.

Uncommon cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy (see section 4.4).

Rare cases of radiation recall have been reported in patients who have received radiotherapy previously (see section 4.4).

Uncommon cases of peripheral ischaemia leading sometimes to extremity necrosis have been reported.

Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.

Rarely, immune-mediated haemolytic anaemia has been reported in patients treated with pemetrexed.

Rare cases of anaphylactic shock have been reported.

Erythematous oedema mainly of the lower limbs has been reported with an unknown frequency. Infectious and non-infectious disorders of the dermis, the hypodermis and/or the subcutaneous tissue have been reported with an unknown frequency (eg. acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis).

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 side effects directly to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, sensory polyneuropathy and rash.

Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia and anaemia. In addition, infection with or without fever, diarrhoea, and/or mucositis may be seen.

In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of calcium folinate / folinic acid in the management of pemetrexed overdose should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

Pharmacotherapeutic group: Folinic acid analogues. ATC code: L01BA04

FINAL PROFESSIONAL INFORMATION

Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate dependent metabolic processes essential for cell replication.

In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even 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 drug action in malignant cells.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of pemetrexed following single-agent administration have been evaluated in 426 cancer patients with a variety of solid tumours at doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 16.1 L. *In vitro* studies indicate that pemetrexed is approximately 81 % bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. 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. In Vitro studies indicate that 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. The pharmacokinetic

properties of pemetrexed are not influenced by concurrently administered cisplatin. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

5.3 Preclinical safety data

Administration of pemetrexed to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate. Administration of pemetrexed to male mice resulted in reproductive toxicity characterised by reduced fertility rates and testicular atrophy. In a study conducted in beagle dog by intravenous bolus injection for 9 months, testicular findings (degeneration/necrosis of the seminiferous epithelium) have been observed. This suggests that pemetrexed may impair male fertility.

Female fertility was not investigated. Pemetrexed was not mutagenic in either the *in vitro*. Chromosome aberration test in Chinese hamster ovary cells, or the Ames test.

Pemetrexed has been shown to be clastogenic in the *in vivo* micronucleus test in the mouse. Studies to assess the carcinogenic potential of pemetrexed have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (E330)

L-Methionine

Monothioglycerol

Sodium Hydroxide(E524) (for pH adjustment)

Hydrochloric acid concentrate(E507) (for pH adjustment)

Water for injections

6.2 Incompatibilities

FINAL PROFESSIONAL INFORMATION

PEMETREXED SOLUTION should ONLY be reconstituted and diluted with 0,9 % Sodium Chloride Injection, without preservative. (see section 6.6).

PEMETREXED SOLUTION is compatible with standard polyvinyl chloride administration sets and intravenous solution bags.

PEMETREXED SOLUTION is physically incompatible with lactated Ringer's Injection and Ringer's Injection.

Co-administration of **PEMETREXED SOLUTION** with other drugs and diluents has not been studied and therefore is not recommended.

6.3 Shelf life

Unopened vial

30 months

Infusion solutions

Chemical and physical in-use stability of infusion solutions of pemetrexed were demonstrated for 24 hours at 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep the vial in the outer carton until required for use.

For storage conditions after dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

PEMETREXED SOLUTION 100 mg/4 ml ACCORD

FINAL PROFESSIONAL INFORMATION

7 ml Type I moulded clear glass vial with Omniflex plus rubber stopper with royal blue flip-off seal.

PEMETREXED SOLUTION 500 mg/20 ml ACCORD

20 ml Type I clear moulded glass vial with Omniflex plus rubber stopper with lavender flip-off seal.

PEMETREXED SOLUTION 850 mg/ 34 ml ACCORD

50 ml Type I clear moulded glass vial with Omniflex plus rubber stopper with plain orange flip-off seal.

PEMETREXED SOLUTION 1000 mg/40 ml ACCORD

50 ml Type I clear moulded glass vial with Omniflex plus rubber stopper with plain red flip-off seal.

Pack of 1 vial

6.6 Special precautions for disposal and other handling

The PEMETREXED SOLUTION for infusion must be prepared as follows:

1. Use appropriate aseptic technique during the reconstitution and further dilution of **PEMETREXED SOLUTION** for intravenous administration.

2. Calculate the dose and number of **PEMETREXED SOLUTION** vials needed. The vial contains an excess of **PEMETREXED SOLUTION** to facilitate delivery of the label amount.

3. **PEMETREXED SOLUTION for infusion must be further diluted with 0,9% Sodium Chloride Injection, without preservative,** prior to intravenous infusion.

Further dilute the appropriate volume of the **PEMETREXED SOLUTION** to 100 ml of 0,9 % Sodium Chloride Injection, without preservative. The bag should be inverted gently to mix the solution to obtain a homogeneous solution.

4. **PEMETREXED SOLUTION** contains no antibacterial preservative. Chemical and physical in-use stability of infusion solutions of pemetrexed were demonstrated for 24 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

FINAL PROFESSIONAL INFORMATION

5. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

6. **PEMETREXED SOLUTION** should then be administered by intravenous infusion over 10 minutes.

7. Procedures for proper handling and disposal should be observed. As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of **PEMETREXED SOLUTION**. Any unused contents of the vial should be discarded.

Preparation and administration precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been few reported cases of pemetrexed extravasation, which were not assessed as serious by the investigator. Extravasation should be managed by local standard practice as with other non-vesicants.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia,

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

PEMETREXED SOLUTION 100 mg/4 ml ACCORD: to be allocated

PEMETREXED SOLUTION 500 mg/20 ml ACCORD: to be allocated

FINAL PROFESSIONAL INFORMATION

PEMETREXED SOLUTION 850 mg/34 ml ACCORD: to be allocated

PEMETREXED SOLUTION 1000 mg/40 ml ACCORD: to be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be confirmed.

10. DATE OF REVISION OF THE TEXT

To be confirmed