1.3.1.1 APPROVED PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form)

ASPEN OXALIPLATIN 50 mg/10 ml (solution for injection)

ASPEN OXALIPLATIN 100 mg/20 ml (solution for injection)

ASPEN OXALIPLATIN 200 mg/40 ml (solution for injection)

COMPOSITION

ASPEN OXALIPLATIN 50 mg/10 ml: Each vial contains 10 ml of aqueous solution equivalent to 50 mg of oxaliplatin.

ASPEN OXALIPLATIN 100 mg/20 ml: Each vial contains 20 ml of aqueous solution equivalent to 100 mg of oxaliplatin.

ASPEN OXALIPLATIN 200 mg/40 ml: Each vial contains 40 ml of aqueous solution equivalent to 200 mg of oxaliplatin.

Excipient: Water for injection.

PHARMACOLOGICAL CLASSIFICATION

A. 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Oxaliplatin is an antineoplastic medicine belonging to a class of platinum-based compounds in which the platinum atom is complexed with 1, 2-diaminocyclohexane ("DACH") and an oxalate group. Oxaliplatin is a single enantiomer, the Cis-[oxalato (trans-λ-1,2-DACH) platinum].
Oxaliplatin exhibits a wide spectrum of both in vitro cytotoxicity and in vivo anti-tumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrates in vitro and in vivo activity in various cisplatin-resistant models.
A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both in vitro and in vivo.
Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the bio-transformation of oxaliplatin interact with DNA to form both inter- and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and anti-tumour effects.

Pharmacokinetic properties

The pharmacokinetics of individual active compounds has not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a 2-hour infusion of oxaliplatin at 130 mg/m^2 every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m^2 every two weeks for 1 to 3 cycles are as follows:

Summary of platinum pharmacokinetic parameter estimates in ultrafiltrate following multiple doses of oxaliplatin at 85 mg/m^2 every two weeks or at 130 mg/m^2 every three weeks

Dose	**C_{max} µg/ml**	**AUC $_{0-48}$ µg.h/ml**	**AUC µg.h/ml**	**$t_{½}$ α h**	**$t_{½}$ ß h**	**$t_{½}$ γ h**	**V_{ss} L**	**CL l/h**
85 mg/m^2								
Mean	0,814	4,19	4,68	0,43	16,8	391	440	17,4
SD	0,193	0,647	1,40	0,35	5 74	406	199	6,35
130 mg/m^2								

Mean	1,21	8,20	11,9	0,28	16,3	273	582	10,1
SD	0,10	2,40	4,60	0,06	2,90	19,0	261	3,07

Mean AUC_{0-48}, and C_{max} values were determined on cycle 3 (85 mg/m^2) or cycle 5 (130 mg/m^2).

Mean AUC, V_{ss}, CL and CLR_{0-48} values were determined on cycle 1.

C_{end}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis. $t_{½}\alpha$, $t_{½}\beta$ and $t_{½}\gamma$ were determined by compartmental analysis (cycles 1 to 3 combined).

At the end of a 2-hour infusion, 15 % of the administered platinum is present in the systemic circulation, the remaining 85 % being rapidly distributed into tissues or eliminated in the urine.

Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin.

No accumulation was observed in plasma ultra-filtrate following 85 mg/m^2 every two weeks or 130 mg/m^2 every three weeks, and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring.

Oxaliplatin undergoes extensive biotransformation in patients, and no intact oxaliplatin was detectable in plasma ultrafiltrate at the end of a 2 hour infusion. Several cytotoxic biotransformation products including the monochloro-, dichloro- and diaquo-DACH platinum species have been identified in the systemic circulation, together with a number of inactive conjugates at later time points.

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours, following administration.

By day 5, approximately 54 % of the total dose was recovered in the urine and < 3 % in the faeces. A significant decrease in clearance from 17,6 ± 2,18 l/h to 9,95 ± 1,91 l/h in renal impairment was observed, together with a statistically significant decrease in distribution volume from 330 ± 40,9 to 241 ± 36,1 l. The effect of severe renal impairment on platinum clearance has not been evaluated.

INDICATIONS

ASPEN OXALIPLATIN in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:

- Treatment of metastatic colorectal cancer
- Adjuvant treatment of colon cancer.

CONTRAINDICATIONS

- History of allergy to oxaliplatin or other platinum compounds
- Myelosuppression prior to starting treatment
- Severe renal impairment (creatinine clearance less than 30 ml/min)
- Pregnancy
- Breastfeeding (see PREGNANCY AND LACTATION)
- Peripheral sensory neuropathy with functional impairment before treatment
- Bone-marrow failure.

WARNINGS AND SPECIAL PRECAUTIONS

Warnings

ASPEN OXALIPLATIN should only be used in specialised departments of oncology and administered under the supervision of an experienced oncologist.

ASPEN OXALIPLATIN may have an antifertility effect, which could be irreversible. Male patients are therefore advised not to father a child up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

Allergic reactions

Allergic reactions are usually managed with standard epinephrine (adrenaline), corticosteroid or antihistamine therapy and require discontinuation of ASPEN OXALIPLATIN therapy. Re-challenge of ASPEN OXALIPLATIN is contraindicated in these patients.

Neurologic toxicity

Reversible posterior leukoencephalopathy syndrome: Reversible posterior leukoencephalopathy syndrome (RPLS, also known as PRES, posterior reversible encephalopathy syndrome) has been observed with the use of ASPEN OXALIPLATIN.

Special precautions

Due to limited information on safety in patients with moderately impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient. In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to ASPEN OXALIPLATIN, the infusion should be immediately discontinued and appropriate symptomatic treatments initiated. ASPEN OXALIPLATIN re-challenge is contraindicated.

In case of ASPEN OXALIPLATIN extravasations, the infusion must be stopped immediately and usual local symptomatic treatment initiated. Sensory peripheral neurological toxicity of ASPEN OXALIPLATIN should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter. For patients who develop acute laryngo-pharyngeal dysaesthesia (see Side effects), during or within the hours following the 2 hour infusion, the next ASPEN OXALIPLATIN infusion should be administered over 6 hours.

To prevent such dysaesthesia, inform the patient to avoid exposure to cold and to avoid ingesting fresh, cold food and/or beverages during or within hours following ASPEN OXALIPLATIN administration.

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended dosage adjustment, based on the duration and severity of the symptoms should be performed:

- If symptoms last longer than seven days and are troublesome, the subsequent ASPEN OXALIPLATIN dose should be reduced from 85 to 65 mg/m2 (metastatic settings) or 75 mg/m^2 (adjuvant settings).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent dose should be reduced from 85 to 65 mg/m^2 (metastatic settings) or 75 mg/m^2 (adjuvant settings).
- If paraesthesia with functional impairment persists until the next cycle, ASPEN OXALIPLATIN should be discontinued.

If these symptoms improve following discontinuation of therapy resumption of therapy may be considered. Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate paraesthesias or paraesthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation of adjuvant setting.

Gastrointestinal toxicity which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see SIDE EFFECTS). Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining ASPEN OXALIPLATIN with 5-fluorouracil.

If haematological toxicity occurs (neutrophils < 1,5 x 109/ ℓ or platelets < 50 x 109/ ℓ), administration of the next course of therapy should be postponed until the haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course.

Patients must be adequately informed of the risk of diarrhoea/emesis and neutropenia after ASPEN OXALIPLATIN 5-fluorouracil administration in order to contact urgently their treating medical practitioner for appropriate management.

If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is ≥ 1,5 x 109/ ℓ .

For ASPEN OXALIPLATIN combined with 5-fluorouracil (with or without folinic acid), the usual dose adjustment for 5-fluorouracil associated toxicities should apply. If severe/life-threatening diarrhoea, severe neutropenia (neutrophils < 1, 0 x 109/ ℓ), severe thrombocytopenia (platelets < 50 x 109/ ℓ) occur, the dose of ASPEN OXALIPLATIN should be reduced from 85 to 65 mg/ m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

In case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, ASPEN OXALIPLATIN should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see SIDE EFFECTS).

In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, rare cases of medicine-induced hepatic vascular disorders should be considered.

Effects on ability to drive and use machines

No studies on the effect of the ability to drive and use machines have been performed. However, ASPEN OXALIPLATIN treatment resulting in an

increase of dizziness, nausea and vomiting and other neurological symptoms that affect gait and balance, may lead to a minor or moderate influence on the ability to drive and use machines.

Vision abnormalities in particular, transient vision loss (reversible following therapy discontinuation) may affect a patient’s ability to drive and use machines. Therefore patients should be warned of the potential effect of these events on the ability to drive, use machines or engage in dangerous activities.

INTERACTIONS

In patients who have received a single dose of 85 mg/m^2 of ASPEN OXALIPLATIN, immediately before administration of 5-fluorouracil, no change in the level of exposure to the 5-fluorouracil has been observed.

In vitro, no significant displacement of oxaliplatin, as contained in ASPEN OXALIPLATIN, binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel and sodium valproate.

Additive bone marrow depression and gastrointestinal adverse events may occur when two or more bone marrow depressants, including radiation are used concurrently or consecutively.

Because normal defence mechanisms may be suppressed by treatment with ASPEN OXALIPLATIN concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus and/or may decrease the patient's antibody response to the vaccine. Immunisation of patients treated with ASPEN OXALIPLATIN should be undertaken with extreme caution.

PREGNANCY AND LACTATION

ASPEN OXALIPLATIN is contraindicated in pregnancy and lactation (see CONTRAINDICATIONS).

Pregnancy

There is no available information on safety of the use in pregnant women. Based on pre-clinical findings, ASPEN OXALIPLATIN is likely to be lethal and/or teratogenic to the human foetus at the recommended therapeutic dose, and is consequently not recommended during pregnancy.

Effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with ASPEN OXALIPLATIN and after cessation of treatment for a period of 4 months in women, and 6 months for men.

Lactation

Excretion in breast milk has not been studied. Breastfeeding is contraindicated during ASPEN OXALIPLATIN therapy (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

FOR ADULTS ONLY

Dosage

Treatment of metastatic colorectal cancer

The recommended dose is 85 mg/m^2 intravenously repeated every 2 weeks.

Adjuvant treatment of colon cancer

The recommended dose is 85 mg/m^2 intravenously repeated every 2 weeks for 12 cycles (6 months). The dosage given should be adjusted according to tolerability (see SIDE EFFECTS).

ASPEN OXALIPLATIN should always be administered before fluoropyrimidines.

ASPEN OXALIPLATIN is administered as a 2 to 6 hour intravenous infusion in 250 to 500 ml of 5 % glucose solution. It is mainly used in combination with continuous infusion 5-fluorouracil based regimens.

Special populations

Renal impairment

ASPEN OXALIPLATIN has not been studied in patients with severe renal impairment (see CONTRAINDICATIONS). In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose (see SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS). There is no need for dose adjustment in patients with mild renal dysfunction.

Hepatic insufficiency

ASPEN OXALIPLATIN has not been studied in patients with severe hepatic impairment. No specific dose adjustment is required in patients with abnormal liver function tests.

Elderly patients

No increase in severe toxicities was observed when oxaliplatin, as contained in ASPEN OXALIPLATIN, was used as a single agent or in combination with 5-fluorouracil in patients over the age of 65. Dosage adjustment is thus not required for the elderly.

Directions for use

ASPEN OXALIPLATIN is administered by intravenous infusion. The administration does not require hyperhydration. ASPEN OXALIPLATIN diluted in 250 to 500 ml of glucose solution to give a concentration of not less than 0,2 mg/ml must be infused either via a peripheral vein or venous line over 2 to 6 hours. ASPEN OXALIPLATIN infusion should always precede that of 5-fluorouracil.

In the event of extravasations, administration must be discontinued immediately.

ASPEN OXALIPLATIN must be diluted before use. Only 5 % glucose diluent is to be used to dilute the concentrate for infusion.

Caution should be exercised with the handling, preparation and disposal of ASPEN OXALIPLATIN.

The preparation of injectable solutions of cytotoxic agents must be carried out by trained personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose.

It is forbidden to eat, smoke or drink in this area. Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protective masks, caps, protective goggles, sterile single use gloves, protective covers for the work area, containers and collective bags for waste.

Excreta and vomit must be handled with care. Pregnant women must be warned to avoid handling ASPEN OXALIPLATIN. Any broken container must be treated with the same precautions and considered as contaminated waste (see below section **Disposal**).

If ASPEN OXALIPLATIN or infusion solution, should come into contact with the skin or mucous membranes wash immediately and thoroughly

with water.

Disposal

Remnants of ASPEN OXALIPLATIN as well as all materials that have been used for reconstitution, dilution or administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws relating to the disposal of hazardous waste.

Incompatibilities

ASPEN OXALIPLATIN must not be used with alkaline medicines or solutions (in particular 5-fluorouracil, basic solutions, trometamol and folinic acid products containing trometamol as an excipient).

ASPEN OXALIPLATIN can be co-administered with folinic acid infusion using a Y-line placed immediately before the site of injection. The medicines should not be placed in the same infusion bag. Flush the line after ASPEN OXALIPLATIN administration.

Do not dilute for infusion with saline solution.

Do not mix with other medicines in the same infusion bag or infusion line.

Do not use injection equipment containing aluminium.

SIDE EFFECTS

Infections and infestations

Frequent: Infection

Blood and the lymphatic system disorders

Frequent: Haemorrhage (nose, rectum), anaemia, neutropenia, thrombocytopenia, leukopenia, lymphocytopenia, leukaemia, febrile neutropenia, neutropenic sepsis, haematuria, thrombophlebitis

Immune system disorders

Frequent: Fever of unknown origin, immune mediated haemolytic anaemia and thrombocytopenia, anaphylactic or anaphylactoid reactions (include bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock)

Metabolism and nutrition disorders

Frequent: Metabolic acidosis

Psychiatric disorders

Frequent: Depression, insomnia

Less frequent: Nervousness

Nervous system disorders

Frequent: Dysaestesia/paraesthesia, peripheral sensory neuropathy, headache, acute neuro-sensory disturbances, dizziness, neuritis motor, meningism, cranial nerve palsies (see details below)

*Less frequent:*Dysarthria, loss of deep tendon reflexes, Lhermitte's sign

Dysaesthesia/paraesthesia of extremities and peripheral sensory neuropathy

The dose limiting toxicity of ASPEN OXALIPALTIN is neurological. It involves a sensory peripheral neuropathy, characterised by peripheral dysaesthesia and/or paraesthesia with or without cramps, often triggered by cold. The symptoms occur in 95 % of patients treated.

The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder and their duration are indications for dose adjustment or even treatment discontinuation.

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of a functional disorder for a

cumulative dose of approximately 850 mg/m^2 (10 cycles) is 10 % and 20 % for a cumulative dose of 1020 mg/m^2 (12 cycles).

In the majority of cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after recovery cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow-up, about 3 % of patients presented either with persisting localised paraesthesias of moderate intensity (2,3 %) or with paraesthesias that interfere with functional activities (0,5 %).

Acute neuro-sensory manifestations

Symptoms usually start within hours of administration and often occur on exposure to cold. They usually present as transient paraesthesia, dysaesthesia and hypoaesthesia. An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1 – 2 % of patients and is characterised by subjective sensations of dysphagia of dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.

Occasionally other symptoms that have been observed included jaw spasm, muscle spasms, involuntary muscle contractions, muscle twitching, myoclonus, abnormal coordination, abnormal gait, ataxia, balance disorders, throat or chest tightness, pressure, discomfort, pain. In addition, cranial nerve dysfunctions may be associated with above mentioned events, or also occur as an isolated event such as ptosis, diplopia, aphonia, dysphonia, hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia, facial pain, eye pain, decrease in visual acuity or visual field disorders.

Eye disorders

Frequent: Conjunctivitis, abnormal vision, abnormal lacrimatio

Less frequent: Decrease of visual acuity, visual field disturbance, optic neuritis

Ear disorders

Frequent: Ototoxicity

Less frequent: Deafness

Vascular disorders

Frequent: Flushing, hypotension, thromboembolism

Respiratory, thoracic and mediastinal disorders

Frequent: Epistaxis, bronchospasm, bronchoconstriction, chest pain, dyspnoea, coughing, rhinitis, pharyngitis, upper respiratory infection, pulmonary embolism, pulmonary fibrosis

Less frequent: Interstitial lung disease

Gastrointestinal disorders

Frequent: Anorexia, nausea, vomiting, diarrhoea, stomatitis, mucositis, abdominal pain, constipation, dehydration, ileus, intestinal obstruction, dyspepsia, gastroesophageal reflux disease, hiccup, flatulence, haemolytic uraemic syndrome, taste perversion

Less frequent: Colitis including *Clostridium difficile* diarrhoea, pancreatitis

Hepato-biliary disorders

Less frequent: Liver sinusoidal obstruction syndrome (also known as veno-occlusive disease of the liver) or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia or perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases

Skin and subcutaneous tissue disorders

Frequent: Alopecia, skin exfoliation (hand and foot syndrome), skin rash, urticaria, erythematous rash, increased sweating, nail disorder.

Musculoskeletal, connective tissue and bone disorders

Frequent: Back pain, arthralgia, skeletal pain, myelosuppression.

Renal and urinary disorders

Frequent: Dysuria, abnormal micturition frequency

Less frequent: Acute tubular necrosis, acute interstitial nephritis and acute renal failure

General disorders and administrative site conditions

Frequent: Fever, rigors (tremors), oedema, chest pain, asthenia, fatigue, weight decrease (metastatic setting), increased weight (adjuvant setting), injection site reaction. Extravasation may result in local pain, inflammation and thrombosis which may be severe and lead to complications including necrosis, especially when ASPEN OXALIPLATIN is infused through a peripheral vein

Investigations

Frequent: Increased alkaline phosphatase, increased bilirubin, glycaemia abnormalities, disturbance of glucose metabolism, increased LDH, hypokalaemia, increased hepatic enzymes ALAT/ASAT), natraemia abnormalities, disturbance of sodium metabolism, increased creatinine

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There is no known antidote to ASPEN OXALIPLATIN. In the case of overdose, exacerbation of adverse events can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment given.

IDENTIFICATION

ASPEN OXALIPLATIN 50 mg/10 ml: A sterile, clear, colourless aqueous solution free from visible particles.

ASPEN OXALIPLATIN 100 mg/20 ml: A sterile, clear, colourless aqueous solution free from visible particles.

ASPEN OXALIPLATIN 200 mg/40 ml: A sterile, clear, colourless aqueous solution free from visible particles.

PRESENTATION

ASPEN OXALIPLATIN 50 mg/10 ml: 20 ml/20 mm type I siliconised clear glass vial with grey bromobutyl omniflex coated rubber closure and grey aluminium flip-off seal.

ASPEN OXALIPLATIN 100 mg/20 ml: 20 ml/20 mm type I siliconised clear glass vial with grey bromobutyl omniflex coated rubber closure and red aluminium flip-off seal.

ASPEN OXALIPLATIN 200 mg/40 ml: 50 ml/20 mm type I siliconised clear glass vial with grey bromobutyl omniflex coated rubber closure and grey aluminium flip-off seal.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Do not freeze. Protect from light. Keep in original container until required for use.

For single use only. Any unused solution should be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

ASPEN OXALIPLATIN 50 mg/10 ml: 45/26/0921

ASPEN OXALIPLATIN 100 mg/20 ml: 45/26/0922

ASPEN OXALIPLATIN 200 mg/40 ml: 45/26/0923

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodland Drive

Woodmead 2191

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