PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

OGIVRI 440 Lyophilised powder for concentrate for solution for infusion

Bacteriostatic Water for Injection for OGIVRI 440 Diluent for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OGIVRI 440: Each multidose vial contains 440 mg trastuzumab.

Reconstituted OGIVRI concentrate contains 21 mg/ml trastuzumab.

Contains sugar: sorbitol 115,2 mg per vial.

Bacteriostatic water for injection for OGIVRI 440: Each vial contains 20 ml sterile bacteriostatic water for injection with 1,1 % *m/v* benzyl alcohol as preservative.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Lyophilised powder for concentrate for solution for infusion.

OGIVRI 440 is an off white to pale yellow, lyophilised powder.

Reconstituted product: colourless to pale yellow solution.

Bacteriostatic Water for Injection for OGIVRI 440: The diluent is a clear colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic breast cancer (MBC)

OGIVRI is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2:

- As monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease.
- In combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- In combination with an aromatase inhibitor for the treatment of patients with hormone-receptor positive metastatic breast cancer.

Early breast cancer (EBC)

OGIVRI is indicated for the treatment of patients with HER2 positive early breast cancer:

- Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- In combination with neoadjuvant chemotherapy followed by adjuvant OGIVRI, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter.

OGIVRI should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. OGIVRI should only be used in patients whose tumours have HER2 overexpression at a 3+ level as determined by immunohistochemistry.

Metastatic gastric-adenocarcinoma (MGC)

OGIVRI in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the

stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

OGIVRI should only be used in patients with metastatic gastric-adenocarcinoma whose tumours have HER2 overexpression as defined by IHC 2+ and a confirmatory silver *in situ* hybridisation (SISH) or fluorescence *in situ* hybridisation (FISH) result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see section 4.4).

In a method comparison study a high degree of concordance (> 95 %) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric-adenocarcinoma patients.

4.2 Posology and method of administration

Posology:

HER2 testing is mandatory prior to initiation of OGIVRI therapy. OGIVRI should be administered as an intravenous infusion. **Do not administer as an intravenous push or bolus.**

Early breast cancer (EBC), Metastatic breast cancer (MBC) and Metastatic gastric-adenocarcinoma (MGC):

Weekly schedule

The following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or docetaxel.

Loading dose

The recommended initial loading dose is 4 mg/kg body weight OGIVRI administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8). Interruption of the

infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses

The recommended weekly dose of OGIVRI is 2 mg/kg body weight, beginning one week after the loading dose. If the loading dose was well tolerated, the subsequent dose can be administered as a 30 [~~90~~]-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8).

In clinical studies, patients were treated with OGIVRI until progression of disease.

Administration in combination with paclitaxel or docetaxel

Paclitaxel or docetaxel may be administered the day following the first dose of OGIVRI or immediately after the subsequent doses of OGIVRI if the preceding dose of OGIVRI was well tolerated.

Early and metastatic breast cancer

Alternative 3-weekly schedule

Initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the prior dosage was well tolerated, the dose can be administered as a 30-minute infusion.

Duration of treatment

Patients with EBC should be treated for 1 year or until disease recurrence.

If the patient misses a dose of OGIVRI by one week or less, then the usual dose of OGIVRI (6 mg/kg) should be given as soon as possible (do not wait until the next planned cycle). Subsequent maintenance OGIVRI doses of 6 mg/kg should then be given every 3 weeks, according to the previous schedule.

Missed doses

If the patient misses a dose of OGIVRI by more than one week, a re-loading dose of OGIVRI should be given (8 mg/kg over approximately 90 minutes). Subsequent maintenance OGIVRI doses of 6 mg/kg should then be given every 3 weeks from that point.

Dose reduction

No reductions in the dose of OGIVRI were made during clinical trials. Patients may continue OGIVRI therapy during periods of reversible, chemotherapy-induced, myelosuppression but they should be monitored carefully for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Special dosage instructions

Elderly

Data suggests that the disposition of trastuzumab, as in OGIVRI, is not altered based on age (see section 5.2). In clinical trials, elderly patients did not receive reduced doses of trastuzumab, as contained in OGIVRI.

Children

OGIVRI is not recommended for use in children below 18 years of age because the safety and efficacy in paediatric patients have not been established.

Method of administration

Handling and disposal

Appropriate aseptic technique should be used.

OGIVRI 440: Each vial of OGIVRI 440 is reconstituted with 20 ml of bacteriostatic water for injection, containing 1,1 % benzyl alcohol. This yields a solution for multiple use, containing 21 mg/ml trastuzumab, at a pH of approximately 6,0. Use of other reconstitution diluents should be avoided.

OGIVRI should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted OGIVRI, may result in problems with the amount of OGIVRI that can be withdrawn from the vial.

Instructions for reconstitution

1. OGIVRI 440: Using a sterile syringe, slowly inject 20 ml of bacteriostatic water for injection in the vial containing the lyophilised OGIVRI 440, directing the stream into the lyophilised cake. Water for injection (not supplied) may also be used for single-dose preparation.

2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes.

The reconstituted preparation results in a colourless to pale yellow transparent solution, free of visible particles.

Instructions for dilution

Determine the volume of the solution required, based on a loading dose of 4 mg trastuzumab per kilogram body weight, or a maintenance dose of 2 mg trastuzumab per kilogram body weight:

Volume (ml) = **Body weight** (kg) x **dose** (4 mg/kg loading or 2 mg/kg maintenance)/21 (mg/ml, concentration of reconstituted solution).

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0,9 % sodium chloride. Dextrose solution should not be used (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral medicine products should be inspected visually for particulates and discolouration prior to administration. Once

the infusion is prepared, it should be administered immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2 - 8 °C.

4.3 Contraindications

- Patients with known hypersensitivity to trastuzumab, murine proteins or to any of the excipients of OGIVRI (see section 6.1). [1, 2]
- Patients with severe dyspnoea at rest due to complications of advanced malignancy or the requirement for supplementary oxygen therapy.
- Pregnancy and lactation, as safety has not been demonstrated.

4.4 Special warnings and precautions for use

Cardiomyopathy

OGIVRI administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with OGIVRI. Discontinuation of OGIVRI treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received trastuzumab, as in OGIVRI, in combination with anthracyclines and cyclophosphamide.

Hypersensitivity reactions including anaphylaxis. Infusion reactions

Pulmonary events

OGIVRI administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions and pulmonary events. These may be fatal. In most cases, symptoms occurred during or within 24 hours of administration of OGIVRI. OGIVRI infusion should be interrupted for patients experiencing dyspnoea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of OGIVRI should be strongly

considered for patients who develop anaphylaxis, angioedema interstitial pneumonitis or acute respiratory distress syndrome.

Embryo-foetal toxicity

Exposure to OGIVRI during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

OGIVRI therapy should only be initiated under supervision of a medical practitioner experienced in the treatment of cancer patients. Refer to blocked warning. The use of OGIVRI and anthracyclines in combination has been associated with a high risk of cardiotoxicity. OGIVRI and anthracyclines should not be used concurrently in combination except in a well-controlled clinical trial setting with cardiac monitoring.

Cardiotoxicity

Signs and symptoms of cardiac dysfunction, such as dyspnoea, increased cough, paroxysmal nocturnal dyspnoea, peripheral oedema, S3 gallop, or reduced ejection fraction, have been observed in patients treated with OGIVRI. Congestive heart failure associated with OGIVRI therapy may be severe and has been associated with disabling cardiac failure, death and mural thrombosis leading to stroke.

Candidates for treatment with OGIVRI, should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: ECG, echocardiogram and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction. A careful risk-benefit assessment should be made before deciding to treat with OGIVRI.

In Early Breast Cancer, the following patients were excluded from the trial; there are no data regarding the benefit: risk balance, and therefore treatment cannot be recommended in such patients:

- History of documented CHF
- High-risk uncontrolled dysrhythmias
- Angina pectoris requiring medication
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction, such as symptomatic heart failure, a history of hypertension or documented coronary heart disease, and in EBC, in those patients with a LVEF of 55 % or less. If LVEF drops 10 ejection points from baseline AND to below 50 %, OGIVRI should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, discontinuation of OGIVRI should be strongly considered, unless the benefits for the individual patients are deemed to outweigh the risks.

Patients receiving OGIVRI should undergo frequent monitoring for deteriorating cardiac function. The probability of cardiac dysfunction was highest in patients who received OGIVRI concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction. Pre-existing cardiac disease or prior cardiotoxicity therapy (e.g. anthracycline or radiation therapy to the chest) may decrease the ability to tolerate OGIVRI therapy: however, the data are not adequate to evaluate the correlation between OGIVRI-induced cardiotoxicity and these factors.

Discontinuation of OGIVRI therapy should be strongly considered in patients who develop clinically significant congestive heart failure. In clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy often including discontinuation of OGIVRI. The safety of continuation or resumption of OGIVRI, in patients who have previously experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of OGIVRI therapy in patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence of clinical deterioration.

Hypersensitivity reactions including anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with OGIVRI. Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most frequently reported in association with the initial infusion.

OGIVRI infusion should be interrupted in all patients with severe hypersensitivity reactions.

In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include epinephrine (adrenaline), corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. There are no data regarding the most appropriate method of identification of patients who may safely be treated with OGIVRI after experiencing a severe hypersensitivity reaction. OGIVRI has been re-administered to some patients who fully recovered from a previous severe reaction. Prior to re-administration of OGIVRI, the majority of these

patients were prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these patients tolerated re-treatment, others had severe reactions despite the use of prophylactic pre-medications.

Infusion reactions

In the post-marketing setting, rare occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of OGIVRI. In clinical trials, infusion reactions consisted of a symptom complex characterised by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumour sites), headache, dizziness, dyspnoea, hypotension, rash, and asthaenia. These reactions were usually mild to moderate in severity (see section 4.8).

However, in post-marketing reports, more severe adverse reactions to OGIVRI infusion were observed and included bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension. These severe reactions were usually associated with the initial infusion of OGIVRI and generally occurred during or immediately following the infusion. However, the onset and clinical course were variable. For some patients, symptoms progressively worsened and led to further pulmonary complications. See “Pulmonary events” below. In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration. Delayed post-infusion events with rapid clinical deterioration have also been reported. Rarely, severe infusion reactions culminated in death within hours or up to one week following an infusion. Some severe reactions have been treated successfully with interruption of the trastuzumab, as in OGIVRI infusion and administration of supportive therapy included oxygen, intravenous fluids, beta-agonist, and corticosteroids.

Interrupt OGIVRI infusion in all patients experiencing dyspnoea, clinically significant hypotension, and intervention of medical therapy administered (which may include

epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate methods of identification of patients who may safely be retreated with OGIVRI after experiencing a severe infusion reaction. Trastuzumab, as in OGIVRI, has been re-administered to some patients who fully recovered from the previous severe reaction. Prior to re-administration of trastuzumab, as in OGIVRI, the majority of these patients were prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these patients tolerated re-treatment, others had severe reactions again despite the use of prophylactic pre-medications.

Pulmonary events

Severe pulmonary events leading to death have been reported with the use of trastuzumab, as in OGIVRI, in the post-marketing setting. Signs, symptoms, and clinical findings include dyspnoea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary oedema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome and pulmonary fibrosis. These events may or may not occur as sequelae of infusion reactions. See “Infusion reactions” above. Patients with symptomatic intrinsic lung disease or with extensive tumour involvement of the lungs, resulting in dyspnoea at rest, may be at greater risk of severe reactions.

Other severe events reported rarely in the post-marketing setting include pneumonitis and pulmonary fibrosis.

Benzyl alcohol

Benzyl alcohol, used as a preservative in bacteriostatic water for injection, has been associated with toxicity in neonates and children up to 3 years old. When administering OGIVRI to a patient with a known sensitivity to benzyl alcohol, OGIVRI should be reconstituted with water for injection, and only one dose per OGIVRI vial should be used. Any unused portion must be discarded.

Sorbitol

Contains sorbitol and may have a laxative effect. Patients with the rare hereditary condition of sorbitol intolerance should not take OGIVRI.

4.5 Interaction with other medicines and other forms of interaction

There has been no formal medicine interaction study performed with OGIVRI in humans. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed. See also section 6.2.

Patients who receive anthracycline after stopping OGIVRI may be at increased risk of cardiac dysfunction because of OGIVRI's long washout period. If possible, medical practitioners should avoid anthracycline based therapy for up to 7 months after stopping trastuzumab products. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

4.6 Fertility, pregnancy and lactation

OGIVRI crosses the placenta and appears in the breast milk (see section 4.3).

OGIVRI can cause foetal harm when administered to a pregnant woman. In post-marketing reports, use of OGIVRI during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

4.7 Effects on ability to drive and use machines

It is not known whether OGIVRI can affect your ability to drive a car or operate machines. However, if during treatment you experience symptoms, such as chills or fever, you should not drive or use machines until these symptoms disappear.

4.8 Undesirable effects

a) Summary of adverse effects

Metastatic breast cancer

OGIVRI can be used at the recommended dose regimen, either as monotherapy, or in combination with paclitaxel. Approximately 65 % of the patients can be expected to experience grade 3 or greater severity adverse reactions. The most common adverse reactions are infusion-related symptoms, such as fever and chills, usually following the first infusion of OGIVRI, nausea, vomiting, diarrhoea, infections, increased cough, headache, fatigue, dyspnoea, rash, neutropenia, anaemia and myalgia.

Adverse reactions that have been reported in association with the use of intravenous trastuzumab, as in OGIVRI, alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting are presented in the table below.

b) Tabulated summary of adverse reactions

System organ class	Adverse reaction	Frequency
	Infection	Frequent

System organ class	Adverse reaction	Frequency
Infections and infestations	Nasopharyngitis	Frequent
	Neutropenic sepsis	Frequent
	Cystitis	Frequent
	Herpes zoster	Frequent
	Influenza	Frequent
	Sinusitis	Frequent
	Skin infection	Frequent
	Rhinitis	Frequent
	Upper respiratory tract infection	Frequent
	Urinary tract infection	Frequent
	Erysipelas	Frequent
	Cellulitis Bronchitis	Frequent Frequent
	Pharyngitis	Frequent
	Sepsis	less frequent
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	frequency unknown
	Neoplasm progression	frequency unknown
Blood and lymphatic system disorders	Febrile neutropenia	Frequent
	Anaemia	Frequent
	Neutropenia	Frequent

System organ class	Adverse reaction	Frequency
	White blood cell count decreased/leukopenia	Frequent
	Thrombocytopenia	frequent
	Hypoprothrombinaemia	frequent
	Immune thrombocytopenia	frequent
Immune system disorders	Hypersensitivity	frequent
	[+]Anaphylactic reaction	frequency unknown
	[+]Anaphylactic shock	frequency unknown
Metabolism and nutrition disorders	Weight decreased/Weight loss	frequent
	Anorexia	frequent
	Hyperkalaemia	frequency unknown
Psychiatric disorders	Insomnia	frequent
	Anxiety	frequent
	Depression	frequent
	Thinking abnormal	frequent
Nervous system disorders	[1]Tremor	frequent
	Dizziness	frequent
	Headache	frequent
	Hypoaesthesia, paraesthesia	frequent
	Dysgeusia	frequent
	Peripheral neuropathy	frequent
	Hypertonia	frequent
	Somnolence	frequent

System organ class	Adverse reaction	Frequency
	Ataxia Lethargy	frequent frequent
	Paresis	less frequent
	Brain oedema	frequency unknown
Eye disorders	Conjunctivitis	frequent
	Lacrimation increased	frequent
	Dry eye	frequent
	Papilloedema	frequency unknown
	Retinal haemorrhage	frequency unknown
Ear and labyrinth disorders	Vertigo Deafness	frequent less frequent
Cardiac disorders	[1] Blood pressure decreased	frequent
	[1] Blood pressure increased	frequent
	[1] Heart beat irregular	frequent
	[1]Palpitation	frequent
	[1]Cardiac flutter	frequent
	Ejection fraction decreased*	frequent
	[+]Cardiac failure (congestive)	frequent
	[+1]Supraventricular tachyarrhythmia	frequent
	Cardiomyopathy Chest discomfort	frequent frequent
	Pericardial effusion	less frequent

System organ class	Adverse reaction	Frequency
	Cardiogenic shock	frequency unknown
	Pericarditis	frequency unknown
	Bradycardia	frequency unknown
	Gallop rhythm present	frequency unknown
Vascular disorders	Hot flush Lymphoedema	frequent frequent
	[+1] Hypotension	frequent
	Vasodilatation Hypertension	frequent frequent
Respiratory, thoracic and mediastinal disorders	[+1]Wheezing	frequent
	[+]Dyspnoea Oropharyngeal pain	frequent frequent
	Cough	frequent
	Epistaxis	frequent
	Rhinorrhoea	frequent
	[+]Pneumonia	frequent
	Asthma	frequent
	Lung disorder Pharyngitis Hiccups Exertional dyspnoea	frequent frequent frequent frequent
	[+]Pleural effusion	frequent
	Pneumonitis	less frequent
	[+]Pulmonary fibrosis	frequency unknown

System organ class	Adverse reaction	Frequency
	[+]Respiratory distress	frequency unknown
	[+]Respiratory failure	frequency unknown
	[+]Lung infiltration	frequency unknown
	[+]Acute pulmonary oedema	frequency unknown
	[+]Acute respiratory distress syndrome	frequency unknown
	[+]Bronchospasm	frequency unknown
	[+]Hypoxia	frequency unknown
	[+]Oxygen saturation decreased	frequency unknown
	Laryngeal oedema	frequency unknown
	Orthopnoea	frequency unknown
	Pulmonary oedema	frequency unknown
	Interstitial lung disease	frequency unknown
Gastrointestinal disorders	Diarrhoea	frequent
	Vomiting	frequent
	Nausea	frequent
	[1] Lip swelling	frequent
	Abdominal pain	frequent
	Dyspepsia	frequent
	Constipation	frequent
	Stomatitis	frequent
	Pancreatitis	frequent
	Haemorrhoids	frequent

System organ class	Adverse reaction	Frequency
	Dry mouth Gastritis	frequent frequent
Hepatobiliary disorders	Hepatocellular injury	frequent
	Hepatitis	frequent
	Liver tenderness Abnormal liver function	frequent frequent
	Jaundice	less frequent
	Hepatic failure	frequency unknown
Skin and subcutaneous tissue disorders	Erythema	frequent
	Rash	frequent
	[1] Swelling face	frequent
	Alopecia	frequent
	Nail disorder	frequent
	Palmar-plantar erythrodysaesthesia syndrome	frequent
	Acne	frequent
	Dry skin	frequent
	Ecchymosis	frequent
	Hyperhydrosis	frequent
	Maculopapular rash	frequent
	Pruritus Onychorrhexis	frequent frequent
	Onychoclasis	frequent

System organ class	Adverse reaction	Frequency
	Dermatitis	frequent
	Urticaria	frequent
	Angioedema	frequency unknown
Musculoskeletal and connective tissue disorders	Arthralgia	frequent
	[1]Muscle tightness	frequent
	Myalgia	frequent
	Arthritis	frequent
	Back pain	frequent
	Bone pain	frequent
	Muscle spasms	frequent
	Neck Pain	frequent
	Pain in extremity Musculoskeletal pain	frequent frequent
Renal and urinary disorders	Renal disorder Dysuria	frequent frequent
	Glomerulonephritis membranous	frequency unknown
	Glomerulonephropathy	frequency unknown
	Renal failure	frequency unknown
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	frequency unknown
	Renal hypoplasia	frequency unknown
	Pulmonary hypoplasia	frequency unknown
Reproductive system and breast disorders	Breast inflammation/mastitis Breast pain	frequent frequent

System organ class	Adverse reaction	Frequency
General disorders and administration site conditions	Asthenia	frequent
	Chest pain	frequent
	Chills	frequent
	Fatigue	frequent
	Influenza-like symptoms	frequent
	Infusion related reaction	frequent
	Pain	frequent
	Pyrexia	frequent
	Mucosal inflammation	frequent
	Peripheral oedema Mucosal inflammation	frequent frequent
	Malaise	frequent
	Oedema	frequent
Injury, poisoning and procedural complications	Nail toxicity Contusion	frequent frequent

+ Denotes adverse reactions that have been reported in association with a fatal outcome

1 Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available

* Observed with combination therapy following anthracyclines and combined with taxanes

The following information is relevant to all indications:

Infusion-related symptoms

During the first infusion with trastuzumab as in OGIVRI, chills and/or fever is frequently observed. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, dizziness, rash, asthenia and hypertension. These symptoms occur infrequently with subsequent OGIVRI infusions. These symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol or an antihistamine such as diphenhydramine. See section 4.2. Some adverse reactions to OGIVRI infusion including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal. See section 4.4.

Hypersensitivity reaction

Anaphylactic reactions were observed less frequently.

Cardiac dysfunction

Congestive heart failure (NYHA Class II – IV) is a common adverse reaction associated with the use of OGIVRI and has been associated with a fatal outcome (see WARNINGS AND SPECIAL PRECAUTIONS). Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop or reduced ejection fraction, have been frequently observed in patients treated with trastuzumab as in OGIVRI. See section 4.4.

Haematotoxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred frequently. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Infection

An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed, in patients treated with OGIVRI.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wp-ontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf or to Imperial Market Access Healthcare South Africa (Pty) Ltd. via email: pvimperiallogistics@dpworld.com.

4.9 Overdose

There is no experience with overdosage in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemis use, other antivirals,

ATC code: J05AX12

OGIVRI 440: A 26 Cytostatic agents

BACTERIOSTATIC WATER FOR INJECTION for OGIVRI 440: A 32.4 Water for injection

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG1 that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to HER2.

The HER2 proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 25-30 % of primary breast cancers.

Trastuzumab has been shown, both in *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. *In vitro*, trastuzumab-mediated, antibody-dependent, cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells, compared with cancer cells that do not overexpress HER2.

5.2 Pharmacokinetic properties

Trastuzumab has dose-dependent pharmacokinetics with a mean elimination half-life of 5,8 days on the 2-mg/kg maintenance dose. Steady state levels are achieved between 16 and 32 weeks, with mean trough and peak concentrations of ~79 and 123 µg/ml, respectively.

Special populations

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Sorbitol

L-histidine

L-histidine hydrochloride monohydrate

Polyethylene glycol 3350

6.2 Incompatibilities

No incompatibilities between OGIVRI and polyvinylchloride or polyethylene or polypropylene bags have been observed.

Dextrose solution should not be used since it causes aggregation of the protein.

OGIVRI should not be mixed or diluted with other medicines.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Vials with lyophilised powder: Store vials at 2–8 °C.

Protect from light.

Reconstituted solution OGIVRI 440:

After reconstitution with bacteriostatic water for injection, the reconstituted solution is physically and chemically stable for 28 days when stored at 2–8 °C. Protect from light.

After reconstitution with bacteriostatic water for injection and infused into PVC bags and PE bags containing 250 ml sodium chloride 0,9 % solution for injection, OGIVRI 440 can be stored at 2–8 °C for 24 hours prior to use. Protect from light.

6.5 Nature and contents of container

OGIVRI 440: Clear 50 ml type 1 glass vial, closed with a grey chlorobutyl rubber stopper coated with fluororesin laminate and sealed with a plastic, plastic, lavender flip-off seal.

Carton containing 1 vial of OGIVRI 440 and 1 vial of Bacteriostatic Water for Injection for OGIVRI 440.

Bacteriostatic Water for Injection for OGIVRI 440: is packed in a clear 20 ml type 1 glass vial, closed with a grey chlorobutyl rubber stopper coated with fluororesin laminate and sealed with a plastic, red flip-off seal.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements. See also section 4.2.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Imperial Market Access South Africa (Pty) Ltd.

Gateway Industrial Park

57 Sarel Baard Crescent

Centurion

South Africa

0157

8 REGISTRATION NUMBERS

OGRIVI 440: 52/26/0216.214

Bacteriostatic Water for Injection for OGIVRI 440

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the registration certificate: 15 May 2019

10 DATE OF REVISION OF THE TEXT

09 September 2024