הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

תאריך 30/03/2014

שם תכשיר באנגלית ומספר הרישום Herceptin vials 440 mg [113-91-29676-00]

שם בעל הרישום רוש פרמצבטיקה (ישראל) בע"מ

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות - עלון לרופא		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). Herceptin treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by healthcare professional only. In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not trastuzumab emtansine. … Breast cancer and gastric cancer *Duration of treatment* Patients with MBC or MGC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first, extending treatment in EBC beyond one year is not recommended (see section 5.1). *Dose reduction* … If left ventricular ejection fraction (LVEF) drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic congestive heart failure (CHF) has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.	HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). Herceptin treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4). Breast Cancer (MBC and EBC) and Metastatic Gastric Cancer (MGC) *Duration of treatment* Patients with MBC or MGC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whatever occurs first. *Dose reduction* …	**4.2 Posology and method of administration**
In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file. … *General considerations* Patients treated with Herceptin are at increased risk for developing CHF) (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel,	… *General considerations* Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin)–containing	**Special warnings and precautions for use**

particularly following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. These may be moderate to severe and have been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.	chemotherapy. This may be moderate to severe and has been associated with death (see section 4.8).	
All candidates for treatment with Herceptin, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin. A careful risk-benefit assessment should be made before deciding to treat with Herceptin. … The safety of continuation or resumption of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF drops ≥10 ejection fraction (EF) points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up. …	All candidates for treatment with Herceptin, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram, or MUGA scan or magnetic resonance imaging. A careful risk-benefit assessment should be made before deciding to treat with Herceptin. … If LVEF drops 10 ejection fraction (EF) points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up. …	
Early breast cancer Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA II –IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with Herceptin and therefore treatment cannot be recommended in such patients. *Adjuvant treatment* … Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low LVEF	*Early breast cancer (EBC)* …	

<table>
<tr>
<td>(<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. In patients receiving Herceptin after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a body mass index (BMI) >25 kg/m^2</td>
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<td>…
Effect of antineoplastic agents on trastuzumab pharmacokinetics
…
The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.</td>
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<td>Interaction with other medicinal products and other forms of interaction</td>
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<td><u>Women of childbearing potential</u>
Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 7 months after treatment has concluded.
…</td>
<td><u>Pregnancy</u>
…
Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 6 months after treatment has concluded.</td>
<td>Fertility, pregnancy and lactation</td>
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<tr>
<td>Tabulated list of adverse reactions
<table>
<tr><th>System organ class</th><th>Adverse reaction</th><th>Frequency</th></tr>
<tr><td>Infections and infestations</td><td>Infection</td><td>Very common</td></tr>
<tr><td rowspan="3">Blood and lymphatic system disorders</td><td>Anaemia</td><td>Very common</td></tr>
<tr><td>Neutropenia</td><td>Very common</td></tr>
<tr><td>White blood cell count decreased/leukopenia</td><td>Very Common</td></tr>
<tr><td rowspan="2">Gastrointestinal disorders</td><td>Dyspepsia</td><td>Very common</td></tr>
<tr><td>Constipation</td><td>Very common</td></tr>
<tr><td rowspan="5">Skin and subcutaneous disorders</td><td>Alopecia</td><td>Very common</td></tr>
<tr><td>Nail disorder</td><td>Very common</td></tr>
<tr><td>Onychoclasis</td><td>Common</td></tr>
<tr><td>Dermatitis</td><td>Common</td></tr>
<tr><td>Urticaria</td><td>Uncommon</td></tr>
<tr><td>Musculoskeletal and connective tissue</td><td>Pain in extremity</td><td>Common</td></tr>
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<tr><td>Nail disorder</td><td>common</td></tr>
<tr><td>Dermatitis</td><td>Not known</td></tr>
<tr><td>Urticaria</td><td>Not known</td></tr>
<tr><td>General</td><td>Mucosal</td><td>common</td></tr>
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<td>Undesirable effects</td>
</tr>
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disorders		
General disorders and administration site conditions	Mucosal inflammation	Very common

Description of selected adverse reactions

Cardiac dysfunction

Congestive heart failure, NYHA II - IV is a common adverse reaction associated with the use of Herceptin and has been associated with a fatal outcome (see section 4.4). Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin (see section 4.4).

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (ie did not receive Herceptin) and in patients who were administered Herceptin sequentially to a taxane (0.3-0.4 %). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0 %). In the neoadjuvant setting, the experience of concurrent administration of Herceptin and low dose anthracycline regimen is limited (see section 4.4).
When Herceptin was administered after completion of adjuvant chemotherapy NYHA class III-IV heart failure was observed in 0.6 % of patients in the one-year arm after a median follow-up of 12 months. After a median follow-up of 8 years the incidence of severe CHF (NYHA III & IV) following 1 year of Herceptin therapy (combined analysis of the two Herceptin treatment arms) was 0.89 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 6.35 %.
Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50 % after the event) was evident for 70 % of Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 83.1 % of Herceptin-treated patients. Approximately 10 % of cardiac endpoints occurred after completion of Herceptin.

In the pivotal metastatic trials of intravenous Herceptin, the incidence of cardiac dysfunction varied between 9 % and 12 % when it was combined with paclitaxel

disorders and administration site conditions	inflammation	

Description of selected adverse reactions

Cardiotoxicity

Cardiotoxicity (heart failure), NYHA II - IV is a common adverse reaction associated with the use of Herceptin and has been associated with a fatal outcome (see section 4.4).

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (ie did not receive Herceptin) and in patients who were administered Herceptin sequentially to a taxane (0.3-0.4%). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0%).

The safety of continuation or resumption of Herceptin in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials (H0648g, H0649g, M77001, BO16216, BO16348, BO18255, B-31, N9831, BCIRG 006, MO16432) improved with standard medical treatment. This included diuretics, cardiac glycosides, beta-blockers and/or angiotensin converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on therapy with Herceptin without additional clinical cardiac events (for information on identification of risk factors and management see section 4.4 .(
In the neoadjuvant setting, the experience of concurrent administration of Herceptin and low dose anthracycline regimen is limited.

compared with 1 % – 4 % for paclitaxel alone. For monotherapy, the rate was 6 % – 9 %. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin concurrently with anthracycline/cyclophosphamide (27 %), significantly higher than for anthracycline/cyclophosphamide alone (7 % – 10 %). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2 % in patients receiving Herceptin and docetaxel, compared with 0 % in patients receiving docetaxel alone. Most of the patients (79 %) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF. … *Infusion reactions, allergic-like reactions and hypersensitivity* It is estimated that approximately 40 % of patients who are treated with Herceptin will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e. during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting, and headache (see section 4.4). The rate of infusion-related reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy. Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of Herceptin (see section 4.4) and have been associated with a fatal outcome. *Anaphylactoid reactions have been observed in isolated cases.*	… *Infusion reactions, allergic-like* reactions and hypersensitivity It is estimated that approximately 40 % of patients who are treated with Herceptin will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e. during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include, but are not limited to, chills, fever, rash, nausea and vomiting, dyspnoea and headache (see section 4.4.(Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of Herceptin (see section 4.4) and have been associated with a fatal outcome .	

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך 02/04/2014

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הודעה על החמרה (מידע בטיחות) בעלון לצרכן

(מעודכן 3102.50)

תאריך

שם תכשיר באנגלית ומספר הרישום

שם בעל הרישום

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות - עלון לצרכן		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
מידע חשוב לעיונך		
לפני השימוש בתרופה		
אזהרות מיוחדות הנוגעות לשימוש בתרופה		
לריאם ותרופות אחרות		
תופעות לוואי		

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך
