Physician knowledge and understanding protocol

Drug Substance	Vandetanib (Caprelsa)
Study Code	D4200N00014
Edition Number	1
Date	01 May 2013

An assessment of physician knowledge and understanding of the risks of vandetanib (Caprelsa®) within the European Union.

Author:
Nigel Soanes, European Medical Information and Patient Safety Director

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

Principal Investigators:

Nigel Soanes
European Medical Information and Patient Safety Director
AstraZeneca
600 Capability Green
Luton
Bedfordshire
LU1 3LU
UK

Jeremy Fazal
Global Business Analyst, Oncology
AstraZeneca
S2/40
2, Kingdom Street
London
W2 6BD
UK

TABLE OF CONTENTS PAGE

LIST OF APPENDICES

1. BACKGROUND

Caprelsa (vandetanib) is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1 of the EU Summary of Product Characteristics[1]).

Caprelsa was approved for use in the European Union on 17 February 2012. At the time of approval it was agreed that AstraZeneca would distribute an educational pack to potential prescribers of Caprelsa to support understanding of the benefit: risk profile of the product.

The educational pack contains:

- The Summary of the Product Characteristics and Package leaflet
- Educational material for physicians
- Patient Alert Cards for patients (with text approved by CHMP)

The educational material for physicians was required to contain the following elements as stated in the European Public Assessment report[1]:

The educational material for Healthcare Professionals should contain the following key elements:

- Vandetanib prolongs the QTc interval and can cause Torsades de pointes and sudden death
- Vandetanib treatment must not be started in patients:
  - Whose ECG QTc interval is greater than 480 msec
  - Who have congenital long QTc syndrome
  - Who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected.
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought.
- Details of medicinal products where the co-administration of vandetanib is either contraindicated or not recommended.
- That vandetanib may cause Posterior reversible encephalopathy syndrome (PRES) also known as Reversible posterior leukoencephalopathy syndrome (RPLS)
- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take
- The role and use of the Patient Alert Card

However, prior to launch in each Member State, AstraZeneca was required to agree with each national competent authority:

- The final content and format of the educational material
- The physician distribution list for the educational pack (to be used at the time of launch and thereafter).

To assess the effectiveness of the educational material, AstraZeneca also committed to implement a survey of prescribers and potential prescribers of Caprelsa.

Therefore, a yearly survey will be performed in each country in the European Union twelve months after Caprelsa is launched and will run for three consecutive years.

If the survey indicates that physicians do not understand or comply with the educational material, a plan will be implemented to further educate physicians and maximise understanding of the risk: benefit profile of the product.

2. OBJECTIVES OF THE KNOWLEDGE AND UNDERSTANDING SURVEY

The study objective is to assess the knowledge and understanding of physicians in relation to the key elements in the Caprelsa educational material.

3. METHODOLOGY

This protocol and the accompanying physician survey were designed by AstraZeneca.

3.1 Study Design

The survey will be conducted in each market in the European Union where Caprelsa is launched. The number of prescribers (or potential prescribers) receiving the material in any one market may be small; therefore a physician may be invited to participate in the survey more than once.

The survey will be a self-administered, internet-based questionnaire accessed through a secure website, instructing the participant to enter a unique code provided in the invitation.

The survey (current draft reflected in Appendix B) will be written to reflect the wording and screen-by-screen presentation of questions for the internet-based survey administration. Completion of the entire survey is expected to take less than 10 minutes.

3.2 Study Population

The educational packs were distributed in accordance with the list of potential Caprelsa prescribers agreed with each national competent authority.

At the time of producing this protocol, the EU countries where Caprelsa has launched/is scheduled to launch includes:

Country	Launch date	Number of educational packs distributed (as of 1 May 2013)
UK	27 February 2012	59
Germany	16 March 2012	2979
Sweden	14 March 2012	4
Finland	16 March 2012	9
Denmark	19 March 2012	4
Austria	29 March 2012	22
Norway	15 May 2012	6
Luxembourg	27 September 2012	81
Netherlands	1 December 2012	690
Belgium	1 May 2013	1975
France	tbc	
Spain	tbc	
Italy	tbc	

A sample of physicians who were targeted to receive the Caprelsa educational pack at the time of launch (and in subsequent months) will be selected to receive an invitation to participate in the survey on an annual basis for three years, the first survey being conducted approximately one year after launch in each market.

Additional screening criteria may be used to determine appropriate participants. Such screening criteria may include but is not limited to:

1. Number of years in practice
2. Treatment of specific number of patients with meduallary thyroid cancer
3. Physician specialty

3.3 Sample Size

The survey will aim to recruit between 15 and 40 physicians from each country included in the project in each year that the fieldwork is being completed. However, there is no fixed sample size for the survey due to two factors:

- The distribution lists for the educational material were targeted to appropriate physicians in each market. In some markets the resultant distribution list was small.

- Considering the targeted nature of the distribution lists, the likelihood of finding respondents for the survey may be reduced.

Taking these practical considerations into account, the distribution lists for the materials will be utilized to initiate physician recruitment and then it will be supplemented with national databases as needed.

The target response rates per market are unknown based on the rarity of the disease. Every effort will be made to maximize response both from the distribution lists and national databases.

4. STUDY PROCEDURES

4.1 Pre-testing of the survey

In order to ensure the questionnaire can be understood by recipients, testing will be performed by two physicians to determine whether there are any items that are not readily understood or where the response may be misinterpreted. The survey will be considered acceptable if no item on the questionnaire is flagged as problematic by both physicians. Revisions to the questionnaire will be recommended based on feedback from the physicians. At that point, the questionnaire in the protocol may be revised. This testing will be done in a single language.

4.1.1 Translation of the survey

Translation will be done after the testing of the questionnaire. All translations to the respective languages will be done using forward and backward translations.

4.2 Survey Administration

Study participants will be directed to a secure website where they will be instructed to enter a unique code to access the survey. Respondents will provide their consent to participate in a study that is designed for market research purposes and not intended to be promotional in any way. Respondents are asked not to share the content of the survey.

In countries where it is the cultural norm, physicians will also be reached by telephone and directed to the questionnaire on the computer.

The data entry system used for the survey will be secure for receiving and storing survey data. Prescriber-identifying information will be stored separately from survey data.

4.3 Recruitment Details

The following describes the steps that will be taken for the recruitment:

1. The distribution lists for the educational materials will be matched to national physician databases held by Adelphi (the market research provider administering the survey on behalf of AstraZeneca)
2. Physicians on the Adelphi databases that match the distribution lists will then be targeted to complete the questionnaire
3. In the event that additional sample is required, national databases held by Adelphi will be used to reach additional sample
4. Screener information will be developed to use for all physicians in the event that this supplementing of sample is necessary

Given the rarity of the disease and the size of the lists, it is understood that recruitment will be challenging. Additional efforts to support recruitment will be considered throughout the study. Efforts may include but are not limited to the following and would require an adjustment of the scope of the project

- Raising the honoraria to increase interest in participation
- Utilizing a custom recruit method to individually research physician contact information
- Other efforts may be discussed as needed

5. ACTIVITIES TO MINIMIZE BIAS IN THE SAMPLE AND QUESTIONNAIRE ADMINISTRATION

Physicians will be initially recruited from the distribution list for the educational material. This section of the sample will therefore reflect the list of prescribers targeted in each market. The initial distribution lists were selected based upon a criteria of "*any oncologist or endocrinologist working at a referral centre for medullary thyroid cancer and who may*

prescribe". However, in some markets this list was supplemented by additional prescribers who AstraZeneca identified as prescribers/potential prescribers post launch or by the national competent authority (for example, the national authority may have specified that all oncologists should receive the materials irrespective of whether they worked at a referral centre).

Any supplementary recruitment required through the national databases held by Adelphi will be made according to the agreed screening criteria.

Basic demographic questions included in the survey will be analysed after the fieldwork is complete, and details of the sample structure made available alongside the survey results.

Physicians who might have access to confidential information about this survey will be excluded (i.e. physicians or their immediate family members who have ever worked for AstraZeneca or a European Regulatory Agency will not be eligible to participate).

An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location. Physicians will be provided with a unique code during the recruitment process and will then be asked to provide the unique code in order to gain access to the online survey. All respondents who are eligible to participate will answer the same questions outlined in appendix B. The code will be inactivated after use to prevent fraud and minimize the chance of a respondent participating in the survey more than once. A reminder notice will be sent to invited participants who have not responded within two to three days of the initial invitation and subsequent contacts may continue to be made to reach the physician.

Physicians may be targeted up to four times, depending on the cultural norm, and then is considered to be uninterested in participating in the research if they do not respond.

6. ANALYSIS

The responses to each survey question will be reported as descriptive statistics. The frequency distribution of responses to each question (the number and percentage of respondents who give answers to each response option) will be presented.

Each question will be evaluated individually.

The following will be reported, as appropriate, as part of this analysis:

- The number of invitations issued to healthcare providers
- The number and percentage of healthcare providers eligible for participation
- The number and percentage of healthcare providers who completed the survey

- Frequency distribution of responses to each survey question (the number of and percentage of respondents who give each answer to each question)

Additional analyses may be performed as needed.

7. TIMELINE

The survey will be performed yearly for three consecutive years in each market where Caprelsa has been launched.

8. REFERENCES

1.

European Public Assessment Report (EPAR), updated 28 February 2013; please note that the EU Summary of Product Characteristics can be found in Annex 1 of the EPAR.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002315/WC500123555.pdf