Table of contents:

Executive Summary

This section provides a concise summary of the most important information contained in the report.

The following information is included as applicable:

- Rationale for the preparation of the report i.e. source of the signal
  -Suggest including relevant information from **Introduction** section
- Product specific information
  - Suggest including relevant information from **Background** section
- Provide information on the event of interest
  - Suggest including relevant information from **Background** section
- Describe all the applicable data sources and methods of evaluation used for the report
  - Suggest including relevant information from **applicable** sections as follows: Toxicology data, clinical studies data, safety database, literature and external databases
- Provide key results as needed
  Suggest including relevant information from **Discussion** section – Summary of important points from the evidence presented in Results section)
- Conclusion statement
  - Suggest including relevant information from **Conclusion** section

1. INTRODUCTION

Include the reason for this topic is being evaluated. Some examples of signal source include:

- Routine signal detection practices
- PRAC request
- New signal identified in PSUR and PBRER
- EU referral
- Regulatory authority request
- Product complaints

2. BACKGROUND

2.1 Product Background

Present the product specific information. **IB** includes the necessary information to include in this section.

The version and date of the reference safety document currently being used must be mentioned.

This section may contain the following information as needed:

- First approval date
- Pharmacology and therapeutic class of drug and mechanism of action
- Available formulation and dosing
- Indications
- Brief description of the population being treated, if relevant

2.1.1 Drug pharmacology

- Pharmacology and therapeutic class of the drug and Mechanism of action (Reference: IB 2.3)
- Available formulation and dosing (Reference: IB 1.2-summarized version, 3.2: detailed version)

For Gavreto (Pralsetinib), the following is the template for this section:

Pralsetinib is a highly potent and selective inhibitor of oncogenic rearranged during transfection (RET) fusion and mutant proteins. RET fusions are oncogenic drivers in 1-2% of NSCLC, 10-20% of papillary thyroid cancer and, at lower prevalence, below 1% across multiple other solid tumor types. Pralsetinib inhibits the ligand independent constitutive activation of the RET tyrosine kinase activity and therefore prevents downstream oncogenic cell signaling.

Pralsetinib was first granted marketing approval in the U.S. on 4 September 2020, which marks the IBD. As of the Data Lock Point (DLP) of the latest Periodic Benefit Risk Evaluation Report (PBRER) (DD Month YYYY), pralsetinib has been approved in 61 countries worldwide. As of September 2024, Pralsetinib has been deregistered in the majority of countries where it was initially authorized, after the decision was taken to discontinue global marketing and development of the program, except in the United States and Greater China. This action was not taken due to any efficacy or safety findings in patients treated with pralsetinib. As of DD Month YYYY, the global safety database and Market Authorization Holder (MAH) status in the EU and US have been transferred from Roche to Blueprint Medicines. Pralsetinib is available as hard capsules and the recommended dose is 400 mg once daily.

2.1.2 Therapeutic Indications

This information can be retrieved from IB (Reference: IB 6.1)

For Gavreto (Pralsetinib), the following is the template for this section:

Non-Small Cell Lung Cancer

Pralsetinib is indicated for the treatment of adult patients with RET fusion-positive, locally advanced or metastatic NSCLC (Gavreto CDS).

Thyroid cancer

Pralsetinib is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic RET-mutant Medullary Thyroid Cancer (MTC) who require systemic therapy and locally advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine refractory (if radioactive iodine is appropriate) (Gavreto CDS).

2.1.3 Patient exposure

This information can be retrieved from PBRER Section 5.

For Gavreto (Pralsetinib), the following is the template for this section:

Since the Developmental International Birth Date (DIBD) (20 December 2016), an estimated total of xxxx patients have received pralsetinib in clinical trial participation. Since the IBD (i.e, 04 September 2020) until DLP of the latest PBRER (DD Month YYYY), an estimated cumulative total of xxxx patients have received pralsetinib from marketing experience. Additionally, a total of xxx patients enrolled and xxx received Pralsetinib through other therapeutic use like pre-approval access, compassionate use programs and expanded access programs

2.2 Event of Interest

- Provide case definition of the event of interest and add the source as well.
- If the event of interest is known for the drugs of same class or competitor molecules, specify that.
- Epidemiology, Risk factors, diagnosis and treatment recommendations - Reference: UptoDate

3 REVIEW OF DATA FROM ALL SOURCES

3.1 Toxicology data:

Toxicology data relevant to the event of interest, if known event in non-clinical studies. **(Reference document: IB Section 4.3.3)**

3.2 Review of clinical studies:

3.3 Review of safety database:

3.3.1 Methodology

A search from DD Month YYYY to DD Month YYYY was performed in the company safety database. This search was performed to identify all solicited (including

interventional clinical trials, non-interventional studies, market research and patient support programs) and unsolicited cases, using Medical Dictionary for Regulatory Activities (MedDRA) version XX.X, coded with the following Preferred Terms (PTs) or High Level Term (HLT) or High Level Group Term (HLGT) and/or Standardized MedDRA Query (SMQ) (narrow/broad)

3.3.2 Results

Stratify the cases as per the following parameters: Source of the report (clinical trials-sponsored and non-sponsored, compassionate use and post-marketing setting -solicited and non-solicited or spontaneous), total no.of events, serious vs non-serious, Grade 3 or higher events, Grade 5 events, causality -related or not related and outcome.

Template:

A total of xx cases (xx events) were reported, of which xx cases were reported from clinical trials (xx from sponsored and xx from non-sponsored trials), xx were reported from compassionate use, and the remaining xxx were from post marketing setting (xx from solicited and xx from spontaneous sources).

Of the xxx events, xx were serious adverse events, of which xx were Grade 4 and xx were Grade 5 events. The most frequently reported PTs were as follows: PT (n=xx), PT (n=xx) ….

Case Narratives for Grade 4 and 5 events

3.4 Literature

3.4.1 Describe the methodology

3.4.2 Results

- Focus on the most relevant publications only
- Identify the following information:
    - Background incidence rates in given population
    - Drugs within the same class (event incidence, safety profile as applicable to assessment)
    - Drugs for the same or similar indication (event incidence, safety profile as applicable to assessment)
- Present the literature by type: epidemiological studies (prospective, then retrospective), published clinical studies, additional case reports.

Template language:

On DD Month YYYY, a literature search was conducted in Medline (DD Month YYYY to DD Month YYYY) and Embase (DD Month YYYY to DD Month YYYY) for articles reporting or discussing the product and safety signal. The following terms were queried:

No relevant publications were retrieved.

OR

The following # relevant literature article (s) was (were) identified and is (are) discussed below.

3.5 Review of external databases (if required)

3.6 Biological plausibility

4 DISCUSSION

5 CONCLUSION

6 REFERENCES

Appendices