VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

GEP-NETS and a fortiori PNETs are rare diseases. The incidence of malignant digestive NETs is around 1/100,000 inhabitants and that the incidence of malignant PNETs is around 0.10-0.15/100,000.
The prevalence of PNETS is estimated around 1.14 / 10,000.

VI.2.2 Summary of treatment benefits

Efficacy in systemic i.v administration
Two comparative randomized trials are available. The first one, published by Moertel in 1992 (Moertel *et al*, 1992) concluded that STZ + doxorubicine (DOX) was more effective than STZ + 5-FU, response rates (RRs) being 69 and 45% respectively. Such results could not be obtained in subsequent studies due to the evolution of efficacy criteria. The second randomized study (Meyer *et al*, 2014) concluded that the STZ + capecitabine association had similar efficacy and less toxicity than the STZ + capecitabine + cisplatin association, with objective response rates of 12% and 16% respectively, and disease control rates (DCR) of 80% and 74% respectively. However, in this study, only 48% of patients had PNETs.

In prospective uncontrolled studies, the RRs reported for the STZ + DOX combination ranged from 21,4% (3/14) in the Frame study in 1988 (Frame *et al*, 1988) to 40% (12/40) in the Fjällskog study) (Fjallskog *et al*, 2008). A prospective non-randomized study published by Eriksson et al. in 1990 (Eriksson *et al*, 1990) compared STZ + DOX and STZ + 5-FU: the STZ + DOX

combination appeared less effective with a 36% (9/25) RR and a 22-month duration of response, as compared to 58% (11/19) and 36 months with STZ + 5-FU.

The STZ + DOX combination has been also evaluated in retrospective studies with very conflicting RRs (from 6% (1/16) in the Cheng (Cheng & Saltz, 1999) or in the Mc Collum study (McCollum *et al*, 2004), to 36% (16/45) in the Delaunoit study (Delaunoit *et al*, 2004). Since these data are retrospective, biases in patients' selection can be suspected (either in treatment assignment or file selection). Despite low RRs, disease control rates were high in some studies: (44% in the Mc Collum study, 62.5% in the Cheng study).

The STZ + 5-FU combination was studied in prospective uncontrolled studies with the following RRs: 38.3% (18/47) in the Turner study (Turner *et al*, 2010) and 52% in a recent French study (STZ + 5-FU + bevacizumab) (Ducreux *et al*, 2014)/ In this study, median progression-free survival was 26.3 months and median overall survival was not reached after a follow-up of 2 years.

In retrospective studies, the RR for the STZ + 5-FU combination was 83.3% (5/6) in the Gonzalez study (Gonzalez *et al*, 2003). The Dilz study (Dilz *et al*, 2015) in 96 patients with PNETs showed a 42.7% RR and a DCR of 83.3%. Median time to progression (TTP) was 19.4 months and median OS was 54.8 months. Finally, in the Antonodimitrakis study (Antonodimitrakis, 2015), the RR was 28% and the DCR was 92%. The median PFS and OS were 23 and 52 months respectively.

VI.2.3 Unknowns relating to treatment benefits

There are no subgroups in which the efficacy has been insufficiently studied and in which efficacy is expected to be different.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Renal toxicity (nephrotoxicity)	Kidneys are a major site of STZ accumulation. Renal impairment is usually dose-related and is evidenced by an increase in plasma urea, creatinine and proteinuria. Renal injury could have consequences ranging from subclinical mild electrolyte / acid-base disturbances to death. However, recently no grade 3 to 5 toxicity was reported in the literature (improvement of patients management before administration)	STZ is contraindicated in patients with pre-existing severe renal failure. Adequate hydration before the administration of STZ may help to reduce the risk of renal impairment. Renal function must be monitored before and after each course of therapy The association with other nephrotoxic drugs must be avoided. (elements mentioned in the product information)

Risk	What is known	Preventability
Hepatic toxicity (Hepatotoxicity)	Some patients have experienced hepatic toxicity, as characterized by elevated liver enzyme (SGOT and LDH) levels and hypoalbuminemia. To be noted that most of these patients in the literature already had liver metastases.	Close monitoring of hepatic functions before, during and after treatment. Monitoring for early symptoms. (elements mentioned in the product information)
Severe nausea and vomiting (gastrointestinal disorders)	Nausea/vomiting is a frequent adverse event, rarely severe with an appropriate prophylaxis	Preventative anti-emetic medicines
Blood count abnormalities (Hematotoxicity)	Bone marrow toxicity of STZ leads to an increased sensitivity to infections which could be severe or life-threatening	Close monitoring of hematologic functions before, during and after treatment (preventability of infections too) (elements mentioned in the product information)
Diabetes or increased levels of sugar in blood (Diabetogenic effect)	Mild to moderate reversible glucose intolerance can occur. Diabetic ketoacidosis occurred after a high number of cycles (28 cycles)	Monitoring of blood glucose levels (elements mentioned in the product information)
Increased sensitivity to infection (immunosuppressive effects)	Immunosuppressive effects of STZ lead to an increase sensitivity to infections which could be severe or life-threatening. Vaccination with live or live-attenuated vaccines can lead to severe / life threatening infection, especially yellow fever vaccine.	Close monitoring of hematologic functions before, during and after treatment Live or live-attenuated vaccine contraindicated.
Post-embolization syndrome in case of off-label use of TACE	In the setting of intra-arterial administration (Trans-Arterial ChemoEmbolization – TACE), a post-embolization syndrome occurs frequently, characterized as nausea, vomiting, abdominal pain, fatigue, fever, and biological abnormalities such as inflammatory response, increases in hepatic enzymes). This syndrome is usually	STZ should not be used for TACE (off-label)

Risk	What is known	Preventability
	transient and is mostly related to the procedure than to the STZ.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Precancerous conditions and Secondary cancers (Mutagenic/carcinogenic effects including Myelodysplastic syndrome (MDS) / acute leukemia (AL) (late hematotoxicity in patients with subsequent PRRT)	Streptozocin is known as a potent alkylating agent highly genotoxic and carcinogenic. These effects were demonstrated in vitro and in vivo. In patients subsequently treated with internal radiotherapy, precancerous conditions until secondary cancer (MDS/AL) could appear very rarely. However, no human case of other non hematological secondary malignancy or hematological secondary malignancy without PRRT was reported in the published literature and no case in which a reasonable possibility of relationship with STZ was reported since the first marketing launch.
Congenital abnormalities following exposure during pregnancy (teratogenicity)	In animals, STZ have effects on foetus (teratogenic effects leading to death in utero), abortifacient effects, lead to premature delivery, prolonged delivery and decrease postnatal survival. Only one pregnant woman was reported to have received STZ during pregnancy (no effect reported for the mother and effects in the baby not reasonably possibly related to STZ)
Impaired fertility	STZ impairs fertility in male and female rats. Only one human case was reported without any information.

Missing information: none

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Streptozocin Keocyt can be found in the Streptozocin Keocyt's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable (there is no studies planned in the post authorisation plan).

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, as it is the first version of the RMP.
Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment

Part VII: Annexes

Annex 1	EudraVigilance Interface
Annex 2	SmPC & Package Leaflet
Annex 3	Worldwide marketing authorisation by country (including EEA)
Annex 4	Synopsis of on-going and completed clinical trial programme
Annex 5	Synopsis of on-going and completed pharmacoepidemiological study programme
Annex 6	Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP part III
Annex 7	Specific adverse event follow-up forms
Annex 8	Protocols for proposed and on-going studies in RMP part IV
Annex 9	Newly available study reports for RMP parts III & IV
Annex 10	Details of proposed additional risk minimisation measures (if applicable)
Annex 11	Mock-up of proposed additional risk minimisation measures (if applicable)
Annex 12	Other supporting data (including referenced material)