6.2 Elements for a Public Summary

6.2.1 Overview of disease epidemiology

Invicorp is to be used for erectile dysfunction, also known as impotence, the inability to get and maintain an erection that is sufficient for satisfactory sexual intercourse, in adult males.

Approximately 10% of men between ages 40-70 have erectile dysfunction, 5% at the age 40 and 15% at age 70. Other studies have found that as much as 45% of men might suffer from erectile dysfunction at some stage. Persons with heart disease, diabetes and hypertension are more likely to suffer from erectile dysfunction. Cigarette smoking by males with heart disease and hypertension also increased the risk of erectile dysfunction. What is clear is that there is a direct relationship between erectile dysfunction and ageing, certain diseases (diabetes, cardiovascular, neurological diseases, depression, chronic renal failure, and pelvic surgery) and lifestyle (smoking and alcohol consumption in particular), and with an inverse relationship to physical activity and education.

6.2.2 Summary of treatment benefits

A number of different pharmaceuticals may be used for treatment of erectile dysfunction and in addition physical and surgical measures such as vacuum pumps and prosthetic implants may be used. The existing therapies for erectile dysfunction may be effective but due to their side effects they may not be optimal for all patients. There are several drugs that may be used for local injection (intracavernosal) and these are considered to be effective for moderate to severe erectile dysfunction .

In studies, the effect of Invicorp is analysed in 1,548 patients. Of these, 759 were treated for six or more months, and 496 for 12 or more months. The results showed that up to 77% of subjects responded to Invicorp compared to a response in up to 18% in subjects receiving placebo treatment. It was found that Invicorp 25 microgram/1 mg was slightly more effective compared to Invicorp 25 microgram/2 mg but this can be explained by the fact that those who received Invicorp 25 microgram/2 mg probably had a more severe disease. There was no evidence of any difference in benefits in patients under or over the age of 60 years or in patients receiving heart medication and no evidence of lower response to the drug over time.

6.2.3 Unknowns relating to treatment benefits

Few studies included men with erectile dysfunction of "psychogenic origin". However, Invicorp is found effective in patients with physical diseases where erectile dysfunction is usually considered difficult to treat, and thus would be expected to be well tolerated and effective in patients with psychogenic erectile dysfunction they less likely to have significant underlying disease.

6.2.4 Summary of safety concerns

6.2.4.1 *Important identified risks*

Risk	What is known	Preventability
Cardiovascular disorder: Tachycardia Palpitations Myocardial infarction Angina pectoris	Heart disease is common in patients with erectile dysfunction. Serious cardiovascular events, such as heart attack, unstable angina and sudden cardiac death have been seen in patients using other products to treat erectile dysfunction. With Invicorp, 6 % of the patients in studies experienced some adverse effects on the heart. However, most of the patients who suffered these events also had additional risk factors. Heart disease and	Instruction not to use product for risk population (contraindication) and warning text in the SmPC and PIL. Invicorp causes vasodilation so it is important that physicians carefully consider the cardiovascular status of their patients and whether those with

	erectile dysfunction has many similar risk factors such as cigarette smoking, dyslipidaemia, hypertension and diabetes mellitus. Therefore, heart disease is common in patients with erectile dysfunction.	significant cardiovascular disease could be at risk especially in combination with sexual activity. According to the Invicorp SmPC caution is advised if Invicorp is used in patients with severe cardiovascular or cerebrovascular disease and the product should not be used (is contraindicated) in men for whom sexual activity is not advisable or for whom that should abstain from sexual activity due to their underlying disease. Furthermore, the SmPC states that treatment with Invicorp should be stopped if tachycardia develops.
Priapism	Priapism is the result of persisting erection (engorgement of the corpora cavernosa) of the penis, caused by disturbance in the mechanisms that control normal erection. Priapism can have various causes including medical conditions and use of certain pharmaceuticals. Sickle cell anaemia, multiple myeloma or leukaemia can predispose men to priapism include. In one study, 38-42% of adult patients with sickle cell disease reported at least one episode of priapism. The overall frequency (incidence) of priapism is 1.5 cases per 100,000 people per year. For men older than 40 years the frequency is higher, 2.9 cases per 100.000 persons per year. Priapism occurred in 0.4 % of patients in the studies. To compare, priapism has been reported in up to11% of patients with other erectile dysfunction therapies. Priapism can be an emergency that may lead to permanent erectile dysfunction and penile	In the SmPC and PIL includes instructions on the injection frequency, instruction not to use product for risk population (contraindication), warning for long term or painful erections and instructions on actions in this case is. The SmPC instructs not to use Invicorp in patients with diseases which may give higher risk of priapism, such as sickle cell anaemia, bone cancer or leukaemia. Also, the SmPC contains a warning that long-term or painful erection may occur, particularly in patients with anatomical deformation of the penis (such as bends, strictured foreskin, cavernous fibrosis, Peyronie's disease or plaque). Furthermore, patients are advised to report each painful or uncomfortable erection that lasts more than 4

	necrosis if left untreated. However, the frequency of priapism with Invicorp is very low and therefore the risk of health effects is very small.	hours to a doctor. Finally, Section 4.9 (Overdose) of the SmPC provides guidance to health care professionals on how to manage priapism if it should occur.
Penile nodules/fibrosis	Scarring of the penis, such as a localised fibrosing of penis (Peyronie's disease) probably results from a combination of predisposing genes and a provoking event, most probably trauma. Peyeronie's disease occurs in up to 9% of men. If patients are not adequately taught how to give their injections, trauma such as injection-site pain and other injection site reactions including bruising and haematoma may occur. Patients who are receiving anticoagulant medication are at an especially high risk of injection site bleeding. In clinical trials with Invicorp, penile nodules/fibrosis occurred in 0.54% of patients. For comparison, fibrosis and irregularity of penis occurred with frequencies up to 2.2% penile fibrotic complications with other injection drugs for erectile dysfunction . Furthermore, a study of patients who developed penile fibrosis while receiving prostaglandin injection showed that the condition improved in over 50% of patients without therapy.	In the SmPC and PIL, instructions on the injection frequency, instruction not to use product for risk population (contraindication), warning against concomitant treatment with anticoagulant and a precaution that Invicorp should not be prescribed without adequate instruction are included.
Injection site reactions (including pain, bruising, haematoma and haemorrhage)	If patients are not taught how to give their injections, injection-site pain and other injection site reactions such as bruising and haematoma may occur. Patients who are receiving anticoagulant medication are at an especially high risk of bleeding at the injection site. However, correct training (as advised in Invicorp SmPC) together with patients becoming more experienced in the injection technique itself will ensure that these reactions	In the SmPC and PIL, instructions on the injection frequency, warning against concomitant treatment with anticoagulant and a precaution that that Invicorp should not be prescribed without adequate instruction are included.

	will not pose a significant concern. In the clinical studies injection site reactions occurred in 24 % of the patients. Penile pain was noted to have occurred only rarely in patients treated with Invicorp on a named patient basis.	

6.2.4.2 *Important potential risk*

No important potential risk has been identified.

6.2.4.3 *Important missing information*

Risk	**What is known**
Liver (Hepatic) impairment	As the product is only used intermittently, has mainly a local effect and is not much take up in the body, the risk in patients with impaired liver is not considered to be high. In the SmPC it is stated that there are no formal studies with these patient groups.
Kidney (Renal) impairment	As the product is only used intermittently, has mainly a local effect and is not much take up in the body, the risk in patients with impaired kidneys is not considered to be high. In the SmPC it is stated that there are no formal studies with these patient groups.
Elderly above 75 years	There are no formal studies in patients above 75 years and this is stated in the patient information. However, in the studies there was no evidence of any difference in effect when comparing patients under the age of 60 years with those over.
Study on effect on the heart rhythm	Invicorp is not taken up in the blood stream in a significant amount and is thus not available to the whole body. The availability of one of the ingredients (phentolamine) to other organs and tissues outside the treatment area is much less than if phentolamine is given directly in the blood stream (intravenously). Furthermore there is nothing to suggest that Phentolamine should effect the heart rhythm. The second ingredient, VIP, is a naturally occurring substance and disappears very rapidly from the body. Consequently, it is not considered that a study concerning heart rhythm is required for this product.

6.2.5 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 for Invicorp can be found in the 2's EPAR page 78.

This medicine has no additional risk minimisation measures

6.2.6 Planned post-authorisation development plan

No additional post authorisation studies or development are planned at this point.

6.2.7 Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1	20-July-2007	Safety Concern 1 Cardiovascular disorders: •Tachycardia •Palpitations •Myocardial infarction •Angina pectoris Safety Concern 2 Reproductive system and breast disorders: Priapism Fibrosis Safety concern 3 General disorder and administration site conditions: -Injection site pain -Application site bruising -Injection site haematoma - Injection site bleeding Important missing information Exposure in special populations: •Hepatic impairment •Renal impairment (not entirely) •Elderly above 75 years (not entirely) •Ethnic groups other than Caucasians	Reference (21).

Version	Date	Safety Concerns	Comment
		ICH E14 compliant QT prolongation Study	
2	15/05/2013	Cardiovascular disorder •Tachycardia •Palpitations •Myocardial infarction •Angina pectoris Priapism Penile nodules/fibrosis Injection site reactions (including pain, bruising, haematoma and haemorrhage) Missing information on exposure in special populations: •Hepatic impairment •Renal impairment •Elderly above 75 years ICH E14 compliant QT prolongation study	The risk management plan RMP Invicorp version 2, has been updated to comply with the "Guideline on good pharmacovigilance practice (GVP) – Module V- Risk management systems" (36). No safety concerns has been added, removed or changed, no studies have been added or finished, and there have been no changes to the risk minimisation activities other than the structural. In section 2.7.3.1, the identified risks 'tachycardia, palpitations, myocardial infarction and angina pectoris' in SOC Cardiac disorders has been grouped as 'Cardiovascular disorder - tachycardia, palpitations, myocardial infarction and angina pectoris' but this is considered an editorial change. The content has been updated with post-marketing data and new literature. Furthermore, the whole document has been revised and restructured according to GVP (36) and new information and sections has been added as required according to GVP. Changes and added information have not been marked with track changes as this was not considered feasible due to the amount of

Version	Date	Safety Concerns	Comment
			editing and the complete restructuring of the document.