Swiss Summary of the Risk Management Plan (RMP) for Intuniv

Retardtabletten
1 mg, 2 mg, 3 mg, 4 mg

Version number CH RMP Summary: 03 (May 2018)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.
The RMP summary of Intuniv is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Intuniv in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Shire Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Intuniv.

This is a summary of the risk management plan (RMP) for Intuniv, Retardtabletten which is based on the EU RMP, version 2.1 of 22 June 2017 which is an international document. Information which is Switzerland specific has been taken into account by referring to the Swissmedic approved "Arzneimittelinformation" (product information), if applicable. Fachinformation = Swiss SmPC and Patienteninformation = Swiss PIL.

1. Overview of disease epidemiology

Intuniv is a medicine to treat attention-deficit hyperactivity disorder (ADHD), a behavioural disorder that involves short attention span and inability to concentrate, restlessness and constant talking and movement, and impulsive behaviour. ADHD is one of the most common behavioural disorders affecting children and adolescents, as it starts during childhood and may continue into adulthood. Individuals with untreated ADHD have higher risk for cigarette smoking and alcohol and substance abuse. Young people with ADHD are also at a higher risk for suicidal behaviour. Attention deficit/ hyperactivity disorder is associated with other mental disorders such as anxiety, depression and learning disability. It is estimated that 5 percent of children 6-17 years have ADHD in Europe. [Ref. EU RMP 2.1, VI.2.1]

2. Summary of treatment benefits

Intuniv contains the active substance guanfacine.

The clinical development program for guanfacine for the treatment of ADHD in children and adolescents included 15 studies conducted in children and adolescents with ADHD. In addition, 12 studies were conducted in healthy adult volunteers. In total, 2882 patients were studied.

The studies demonstrated that all doses of guanfacine (1 to 7 mg daily) were effective. General improvement in the patient's ADHD was measured using questionnaires that were completed by the patient's doctor, parents and teachers. Specific symptoms of ADHD also improved for hyperactivity/impulsivity and inattentiveness.

Guanfacine was shown to be effective in 6 short term, studies. In addition, results from 2 long-term studies suggested that guanfacine was effective for up to 24 months of treatment.

There were no differences in the effectiveness between males and females or between ethnic groups or races. [Ref. EU RMP 2.1, VI.2.2]

3. Unknowns relating to treatment benefits

There is little or no information on the use of this medicine in pregnant women, children with liver or kidney disease, or children under 6 years of age. [Ref. EU RMP 2.1, VI.2.3]

4. Summary of safety concerns

Table 1: Summary of Safety Concerns [Ref. EU RMP 2.1, VI.1.1, Table 53]	
Important identified risks	• Bradycardia • Syncope • Hypotension/decreased blood pressure • Withdrawal blood pressure increase • Sedative events • Weight increase
Important potential risks	• Cardiac valvulopathy • QT prolongation • Off-label use • Blood glucose disorder
Missing information	• Use in pregnant or breastfeeding women • Use in patients with hepatic or renal impairment • Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)

4.1 Important identified risks

Table 2: Important Identified Risks [Ref. EU RMP 2.1, VI.2.4, Table 56]		
Risk	**What is Known**	**Preventability**
Slow heart beat (bradycardia)	In studies to license the medicine most cases of slow heart beat did not require any treatment and resolved.	Heart rate and blood pressure should be measured before starting treatment and then every week while the dose is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year See **Fachinformation** (= Swiss SmPC), Section "Dosage and administration" under *"Pre-treatment Screening".* See **Patienteninformation** (=Swiss PIL) under Section: **When should Intuniv be used with caution?/ Wann ist bei der Einnahme von Intuniv® Vorsicht geboten?** *"Talk to your doctor or pharmacist before taking this medicine if:* • *you have low blood pressure, heart problems or have a family history of heart problems* • *you have fainted recently …* *If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking this medicine. This is because this medicine can make these problems worse. Your doctor will routinely monitor you to see how this medicine affects you.* … *Other medicines and Intuniv*

Table 2: Important Identified Risks [Ref. EU RMP 2.1, VI.2.4, Table 56]		
Risk	**What is Known**	**Preventability**
		Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Intuniv and some other medicines can affect each other. *Tell your doctor or pharmacist if you* • *suffer from other diseases,* • *have any allergies, or* • *are taking other medicines (including those you may have bought yourself!)* *In particular, tell your doctor or pharmacist if you are taking any of the following [types of] medicines:* • *medicines that lower your blood pressure (antihypertensives)* • *medicines for epilepsy such as valproic acid* • *medicines that make you sleepy (sedatives)* • *medicines for mental health problems (benzodiazepines, barbiturates and antipsychotics)* • *medicines that can affect the way Intuniv is eliminated by the liver (please see table below)"*
Fainting (syncope)	In clinical studies most cases of fainting did not require treatment and resolved. However, fainting suddenly can result in a fall and injury	Heart rate and blood pressure should be measured before starting treatment and then every week while the dose is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year See **Fachinformation** (= Swiss SmPC), Section "Dosage and administration" under *"Pre-treatment Screening".* See **Patienteninformation** (=Swiss PIL) under Section: **When should Intuniv be used with caution? / Wann ist bei der Einnahme von Intuniv® Vorsicht geboten?**
Low blood pressure (hypotension/decreased blood pressure)	In clinical studies most cases of low blood pressure did not require any treatment and resolved.	Heart rate and blood pressure should be measured before starting treatment and then every week while the dose is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year See **Fachinformation** (= Swiss SmPC), Section "Dosage and administration" under

Table 2: Important Identified Risks [Ref. EU RMP 2.1, VI.2.4, Table 56]		
Risk	**What is Known**	**Preventability**
		"Pre-treatment Screening". See **Patienteninformation** (=Swiss PIL) under Section: **When should Intuniv be used with caution?/Wann ist bei der Einnahme von Intuniv® Vorsicht geboten?**
High blood pressure when the medicine is stopped suddenly (withdrawal blood pressure increase)	Stopping this medicine suddenly can cause the blood pressure to increase, a so-called withdrawal effect. The increase is generally not serious but there is a risk for more severe increase in blood pressure if a patient has had high blood pressure in the past.	When stopping treatment with Intuniv, it is recommended that the dose is reduced gradually to minimise the likelihood of withdrawal effects. See **Fachinformation** (= Swiss SmPC), Section "Dosage and administration" See **Patienteninformation** (=Swiss PIL) under Section: **How do you take Intuniv?/ Wie verwenden sie Intuniv®?** *"If you stop taking Intuniv* Do not stop taking this medicine without first talking to your doctor. • If you stop taking this medicine your blood pressure and heart rate may increase. • To stop the medicine, your doctor will slowly reduce your Intuniv dose to minimise any side effects"
Drowsiness possibly with slowing down of breathing and heart rate (sedative events)	In clinical studies most cases of sleepiness did not require any treatment and resolved. However, sleepiness can be severe and may result in an accident and injury.	Patients should be closely monitored weekly while the dose is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year. See **Fachinformation** (= Swiss SmPC), Section "Dosage and administration" under *"Pre-treatment Screening".* See **Patienteninformation** (=Swiss PIL) under Section: **How do you take Intuniv?/ Wie verwenden sie Intuniv®?** *"If you stop taking Intuniv …"*
Weight increase	In long-term clinical studies the body mass index (BMI) of a small number of patients increased 12 months after starting this medicine compared to when they began receiving it. BMI indicates if a person is of healthy weight; an increase in BMI suggests that the person is putting on extra weight.	As part of routine monitoring height, weight and BMI should be monitored. It is important for the patient to tell the doctor or pharmacist about any problem with weight before taking this medicine. See **Fachinformation** (= Swiss SmPC), Section "Warnings and precautions" under *"Effects on height, weight and Body Mass index (BMI)"* See **Patienteninformation** (=Swiss PIL) under Section: **When should Intuniv be used with caution?/ Wann ist bei der Einnahme von Intuniv® Vorsicht geboten?**

ADHD=attention deficit/ hyperactivity disorder; BMI=body mass index

4.2 Important potential risks

Table 3: Important Potential Risks [Ref. EU RMP 2.1, VI.2.4, Table 57]	
Risk	**What is Known**
Disease of the heart valves (cardiac valvulopathy)	There were no reports of cardiac valvulopathy in clinical studies or after marketing
Alteration of the electrical activity of the heart (QT interval prolongation)	In clinical studies, there was no case of serious QT interval prolongation and most were moderate in severity and resolved.
Use of the medicine in a way that is not covered by the medicine's product information (off-label use)	This medicine has not been studied in children under age 6 years, adults and the elderly.
Blood sugar disorder (Blood glucose disorder)	In clinical studies, most cases of blood glucose disorder were mild in severity.

4.3 Missing information

Table 4: Missing Information [Ref. EU RMP 2.1, VI.2.4, Table 58]	
Use in pregnant or breast-feeding women	There is no information on the use of this medicine in pregnant or breastfeeding women.
Use in patients with liver or kidney disease	There is no information on the use of this medicine in patients with liver or kidney disease.
Long-term safety especially effects on growth, sexual maturation and mental processes such as thinking, learning and memory in particular parts of the brain (neurocognition)	There is limited information about the effects of this medicine with long term use.

5. Summary of risk minimisation measures by safety concern

All medicines have an SmPC (Fachinformation), which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in plain language is provided in the form of the package leaflet (Patienteninformation). The measures in these documents are known as routine risk minimisation measures.

Additionally Shire (the company that makes Intuniv) has developed educational materials for healthcare professionals to address the risks of: Bradycardia, syncope, hypotension/decreased blood pressure, withdrawal blood pressure increase, sedative events, and weight increase. The educational materials were developed to remind healthcare professionals about the screening to be performed before deciding if the patient is a candidate to receive Intuniv and on the examinations to be performed periodically during treatment. [Ref. EU RMP 2.1, VI. 2.5]

Table 1: Summary of Risk Minimisation Measures [EU RMP 2.1, VI.1.4, Table 55]

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Bradycardia	Prescreening, during titration and ongoing monitoring stipulation in Section "Dosage and administration" of the Fachinformation (Swiss SmPC). The Section "Warnings and precautions" of the proposed Fachinformation (Swiss SmPC) advises assessing patient's cardiovascular status prior to initiation of treatment, weekly during dose titration and stabilisation, at least every 3 months for the first year, taking into consideration clinical judgment, and 6 monthly thereafter, with more frequent monitoring following any dose adjustment. Caution when treating patients with a history of hypotension, heart block, bradycardia or cardiovascular disease. Caution when treating patients with a history of syncope or a condition that may predispose to syncope. Caution when treating patients concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. The Section "Interactions" of the proposed Fachinformation (Swiss SmPC) recommends using caution when INTUNIV is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors. Bradycardia is listed as an ADR in Section "Undesirable Effects" of the proposed Fachinformation (Swiss SmPC).	Educational materials for Healthcare professionals
Syncope	Prescreening, during titration and ongoing monitoring stipulation in Section "Dosage and administration" of the Fachinformation (Swiss SmPC). Section "Warnings and precautions" of the proposed Fachinformation (Swiss SmPC) advises assessing patient's cardiovascular status prior to initiation of treatment, weekly during dose titration and stabilisation, at least every 3 months for the first year, taking into consideration clinical judgment, and 6 monthly thereafter, with more frequent monitoring following any dose adjustment. Caution when treating patients with a history of hypotension, heart block, bradycardia or cardiovascular disease. Caution when treating patients with a history of syncope or a condition that may predispose to syncope. Caution when treating patients concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Section "Interactions" of the proposed Fachinformation (Swiss SmPC) recommends using caution when INTUNIV is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors. Section "Effects on ability to drive and use machines" warns of possible effects on the ability to drive and use machines. Syncope is listed as an ADR in Section "Undesirable	Educational materials for Healthcare professionals

Table 1: Summary of Risk Minimisation Measures [EU RMP 2.1, VI.1.4, Table 55]

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Effects" of the proposed Fachinformation (Swiss SmPC).	
Hypotension/decreased blood pressure	Prescreening, during titration and ongoing monitoring stipulation in Section "Dosage and administration" of the Fachinformation (Swiss SmPC). Section "Warnings and precautions" of the proposed Fachinformation (Swiss SmPC) advises assessing patient's cardiovascular status prior to initiation of treatment, weekly during dose titration and stabilisation, at least every 3 months for the first year, taking into consideration clinical judgment, and 6 monthly thereafter, with more frequent monitoring following any dose adjustment. Caution when treating patients with a history of hypotension, heart block, bradycardia or cardiovascular disease. Caution when treating patients with a history of syncope or a condition that may predispose to syncope. Caution when treating patients concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Section "Interactions" of the proposed Fachinformation (Swiss SmPC) recommends using caution when Intuniv is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors. Hypotension and blood pressure decreased are listed as ADRs in Section "Undesirable effects" of the proposed Fachinformation (Swiss SmPC).	Educational materials for Healthcare professionals
Withdrawal blood pressure increase	Section "Dosage and administration" of the proposed Fachinformation (Swiss SmPC) recommends monitoring blood pressure and pulse during dose downward titration (decrements of no more than 1mg every 3 to 7 days) and following discontinuation of Intuniv. Blood pressure and pulse should be monitored when reducing the dose or discontinuing Intuniv (Section "Warning and precautions"). Hypertension, blood pressure increased and hypertensive encephalopathy are listed as ADRs in Section "Undesirable effects" of the proposed Fachinformation (Swiss SmPC).	Educational materials for Healthcare professionals
Sedative events	Prescreening, during titration and ongoing monitoring stipulation in Section "Dosage and administration" of the Fachinformation (Swiss SmPC). Section "Warning and precautions" of the proposed Fachinformation (Swiss SmPC) advises monitoring patients weekly during dose titration and stabilisation, and every 3 months during the first year, taking into consideration clinical judgment Section "Interactions" of the proposed Fachinformation (Swiss SmPC) recommends using caution when INTUNIV is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors.	Educational materials for Healthcare professionals

Table 1: Summary of Risk Minimisation Measures [EU RMP 2.1, VI.1.4, Table 55]		
Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
	Section “Effects on ability to drive and use machines” warns of possible effects on the ability to drive, use machines or cycling. Sedative events (somnolence, sedation, hypersomnia) are listed as ADRs in Section “Undesirable Effects” of the proposed Fachinformation (Swiss SmPC).	
Weight increase	Prescreening, during titration and ongoing monitoring stipulation in Section “Dosage and administration” of the Fachinformation (Swiss SmPC). Section “Warnings and precautions” of the proposed Fachinformation (Swiss SmPC) recommends monitoring of height, weight and BMI prior to initiation of therapy and then every 3 months for the first year, taking into consideration clinical judgement. 6 monthly monitoring should follow thereafter, with more frequent monitoring following any dose adjustment. Weight increased is listed as an ADR in Section “Undesirable effects” of the SmPC.	Educational materials for Healthcare professionals
Cardiac valvulopathy	None	None
QT prolongation	Prescreening, during titration and ongoing monitoring stipulation in Section “Dosage and administration” of the Fachinformation (Swiss SmPC): “Examinations recommended before the start of treatment Prior to prescribing Intuniv, it is necessary to conduct a baseline evaluation to identify patients at increased risk of somnolence and sedation, hypotension and bradycardia,QT-prolongation arrhythmia, and weight increase/risk of obesity. A cardiovascular examination, including measurement of blood pressure and heart rate, must be carried out and documented together with a comprehensive history of concomitant medications, past and present, co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death. As no long-term data are available, regular cardiovascular examinations must be carried out in the event of risk factors (see section “Warnings and precautions”).” Section “Warning and precautions”: “The effect of 2 dose levels of immediate-release guanfacine (4 mg and 8 mg) on QT interval was evaluated in a double-blind, randomized, placebo- and active-controlled, cross-over study in healthy adults. An apparent increase in mean QTc was observed for both doses. This finding has no known clinical relevance. Guanfacine does not interfere with cardiac repolarization of the form associated with pro-arrhythmic drugs.”	None

Table 1: Summary of Risk Minimisation Measures [EU RMP 2.1, VI.1.4, Table 55]

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Off-label use	Use in children under 6 years, Adults and Elderly is addressed in Section "Dosage and administration" (Special populations) of the proposed Fachinformation (Swiss SmPC).	None
Blood glucose disorder	None	None
Use in pregnant or breastfeeding women	Pregnancy and breastfeeding are addressed in Section "Pregnancy and lactation" of the proposed Fachinformation (Swiss SmPC)	None
Use in patients with renal or hepatic impairment	Use in patients with renal or hepatic impairment is addressed in Section "Dosage and administration" (Special populations) of the proposed Fachinformation (Swiss SmPC).	None
Long-term safety(neurocognition in particular, but also effects on growth, sexual maturation)	Long-term safety is addressed in Section "Dosage and administration" of the proposed Fachinformation (Swiss SmPC).	None

ADR=adverse drug reaction; BMI=body mass index; SmPC=Summary of Product Characteristics → Swiss version: referred to as "Fachinformation"

6. Planned post-authorisation development plan

6.1 List of studies in post authorisation development plan

Table 6: List of Studies in Post-authorisation Development Plan [EU RMP 2.1, VI.2.6, Table 59]

Study/Activity (including study number)	Objectives	Safety Concerns/Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and) Final Results
Drug utilisation study of INTUNIV (guanfacine extended release) in the European Union (Category 3)	**Primary objective:** To characterise patients who are prescribed guanfacine. To describe prescribing patterns of guanfacine among physicians **Secondary objective:** To measure the effectiveness of the educational materials for healthcare professionals in order to assess compliance with the indication and with visits and measurements needed during the first	Off-label use. Effectiveness of the educational materials for healthcare professionals	Started	Annual reports planned first year after approval (to coincide with PSUR)

Table 6: List of Studies in Post-authorisation Development Plan [EU RMP 2.1, VI.2.6, Table 59]				
Study/Activity (including study number)	**Objectives**	**Safety Concerns/Efficacy Issue Addressed**	**Status**	**Planned Date for Submission of (Interim and) Final Results**
	year of treatment.			
SHP503-401: A Comparative Safety Study of Intuniv in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) according to an agreed protocol (Category 1)	**Primary objective:** To investigate the long-term safety especially effects on neurocognition (assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) or any other scale as per current clinical guidelines. **Secondary objectives:** To further characterise the risks of hypotension, syncope, sedative events, weight increase, bradycardia growth, sexual maturation and QT prolongation.	Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	Planned	~~Submission of~~ Protocol submitted: 22 July 2016 Submission of final study report: 31 Jan 2022

6.2 Studies which are a condition of the marketing authorisation

Study SHP503-401 is a condition of the marketing authorisation. [Ref. EU RMP 2.1, VI.2.6.1]

6.3 Ongoing and Planned Studies in the Post authorization Pharmacovigilance Development Plan

Table 7: Overview of Ongoing and Planned Studies [Ref. EU RMP 2.1, Table 54]				
Study/Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
Drug utilisation study of INTUNIV (guanfacine extended release) in the European Union (Category 3)	**Primary objective:** To characterise patients who are prescribed guanfacine. To describe prescribing patterns of guanfacine among physicians **Secondary Objective:** To measure the effectiveness of the additional risk	Off-label use Effectiveness of the educational materials for healthcare professionals	Started	Annual reports planned starting first year after approval (to coincide with PSUR)

Table 7: Overview of Ongoing and Planned Studies [Ref. EU RMP 2.1, Table 54]				
Study/Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
	minimisation measure (educational materials for healthcare professionals) in order to assess compliance with the indication and with visits and measurements needed during the first year of treatment.			
SHP503-401: A Comparative Safety Study of Intuniv in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) according to an agreed protocol (Category 1)	**Primary objective:** To investigate the long-term safety especially effects on neurocognition (assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) or any other scale as per current clinical guidelines. **Secondary objectives:** To further characterise the risks of hypotension, syncope, sedative events, weight increase, bradycardia, growth, sexual maturation and QT prolongation.	Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	Planned	Submission of protocol: 31 July 2016 Submission of final study report: 31 Jan 2022

ADHD=attention-deficit/hyperactivity disorder; CANTAB=Cambridge Neuropsychological Test Automated Battery; PSUR=Periodic Safety Update Report

7. Summary of changes to the Risk Management Plan over time

Table 8: Major Changes to the Risk Management Plan Over Time [Ref. EU RMP 2.1, Table 60]			
Version	**Date**	**Safety Concerns**	**Comments**
1.5	22 Jul 2015	**Important Identified risks** • Bradycardia • Syncope • Hypotension/decreased blood pressure • Withdrawal blood pressure increase • Sedative events • Weight increase	First submitted version

		Important Potential risks • Cardiac valvulopathy • QT prolongation • Off-label use • Blood glucose disorder **Missing Information** • Use in pregnant or breast-feeding • women • Use in patients with hepatic or renal • Impairment • Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation) • Drug interactions	
2.0	14 Nov 2016	Removed 'Drug interactions' as missing information Otherwise, same as 1.5.	Updated to include results from clinical study SPD503-318, nonclinical studies (V7400MSPD503, V7401M-SPD503, V7089M-SPD503, V7613MSPD503) Inclusion of additional SmPC text addressing 'withdrawal blood pressure increase'
2.1	22 Jun 2017	Same as 2.0	Updated to address comments from assessment of RMP: -Listed all key elements of the educational materials in table 51; removed texts in section IV.1 and table 26.