Swiss Summary of the Risk Management Plan (RMP)

BOTOX®

(Botulinum toxin type A)

50/100/200 Allergan Units

Powder for solution for injection

Version 2 (06 September 2023)

Based on RMP, version 9.5, dated 14 July 2022

AbbVie AG, Cham

Disclaimer

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 minimize them. The RMP summary of BOTOX® 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 BOTOX in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AbbVie AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of BOTOX.

Part VI: Summary of the Risk Management Plan

This is a summary of the risk management plan (RMP) for BOTOX®. The RMP details important risks of BOTOX®, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information).
The summary of product characteristics (SmPC) for BOTOX® and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how BOTOX® should be used. Important new concerns or changes to the current ones will be included in updates of the BOTOX® RMP.

I. The Medicine and What it Is Used For

BOTOX® is authorised for the following indications (see SmPC for the full indications):

- Symptomatic treatment of blepharospasm, hemifacial spasm (HFS), and associated focal dystonias:
    - Symptomatic relief of blepharospasm, HFS, and idiopathic cervical dystonia (CD) (spasmodic torticollis [**UK**])
    - Treatment of blepharospasm, HFS, and spasmodic torticollis (**France**)
- Symptomatic treatment of CD (spasmodic torticollis)
- Symptomatic treatment of Focal spasticity of:
    - elbow, wrist and hand in paediatric cerebral palsy patients, two years of age or older as an adjunct to rehabilitative therapy (**UK**)
    - the ankle and foot in ambulant paediatric cerebral palsy patients, two years of age or older as an adjunct to rehabilitative therapy
    - focal spasticity of the upper limb (wrist, hand and elbow) in adult post stroke patients
    - the ankle and foot in adult post stroke patients
    - the wrist and hand disability due to upper limb spasticity associated with stroke in adults (**UK**)
    - the ankle and foot disability due to lower limb spasticity associated with stroke in adults (**UK**)
- Local symptomatic treatment of spasticity (muscular overactivity) in upper and/or lower limbs in adults and children 2 years old and over (**France**)
- Management of persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment
- Management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics (**UK**)
- Persistent severe hyperhidrosis of the axillae, resistant to topical treatment and which has an important psychological and social impact (**France**)
- Symptom relief in adults fulfilling criteria for chronic migraine (CM) (headaches on ≥ 15 days per month of which ≥ 8 days with migraine) in patients who have responded inadequately or are intolerant of prophylactic migraine medications
- Prophylaxis of headaches in adults with CM (headaches on ≥ 15 days per month of which ≥ 8 days are with migraine) (**UK**)
- Prophylactic treatment of CM (presence of headache at least 15 days per month including at least 8 days per month with migraine) in adult patients who have not responded or are intolerant to other prophylactic treatments for migraine (**France**)

- Temporary improvement in the appearance of the following facial lines, when the severity of these lines has an important psychological impact on adult patients:
    - moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines)
    - moderate to severe lateral canthal lines (crow's feet lines [CFL]) seen at maximum smile
    - moderate to severe CFL seen at maximum smile and glabellar lines seen at maximum frown when treated simultaneously (**UK, Czech Republic, Poland, Slovakia**)
    - moderate to severe forehead lines (FHL) associated with frontalis muscle activity (**UK, Poland**)
- Oculomotor disorders: Strabismus, recent oculomotor paralysis, recent dysthyroid ocular myopathy in adults and children over 12 years old (**France**)
- Management of bladder disorders
    - Idiopathic overactive bladder (OAB) with symptoms of urinary incontinence (UI), urgency, and frequency, in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication
    - Urinary incontinence in adults with neurogenic detrusor overactivity (NDO) resulting from neurogenic bladder due to stable subcervical spinal cord injury (SCI), or multiple sclerosis (MS)
- Management of bladder dysfunction in adult patients who are not adequately managed with anticholinergics (**UK**)
    - overactive bladder with symptoms of UI, urgency, and frequency
    - neurogenic detrusor overactivity with UI due to subcervical SCI (traumatic or non-traumatic) or MS
- Bladder dysfunction in adult patients (**France**):
    - Treatment of NDO leading to UI not adequately managed by anticholinergic therapy:
        - in patients with SCI
        - in patients with MS and using clean intermittent catheterisation (CIC) for emptying their bladder
    - Treatment of idiopathic OAB associated with symptoms including:
        - 3 UI episodes with urgency within 3 days and
        - Urinary frequency defined as 8 or more voids/day in patients who do not adequately respond to anticholinergic medication (after 3 months of treatment) or are intolerant of anticholinergic medication and do not respond to a well-performed physiotherapy

BOTOX® contains *Clostridium botulinum* type A neurotoxin as the active substance and it is given by injection.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of BOTOX®, together with measures to minimise such risks and the proposed studies for learning more about the risks of BOTOX®, are outlined below:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of BOTOX® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BOTOX®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Important identified risks	**All Indications**
	Pre-existing neuromuscular disorders
	Immunogenicity, drug resistance, and antibody formation
	Distant spread of toxin
	Neurology Indications
	Dysphagia in Cervical Dystonia and in Chronic Migraine patients
Important potential risks	**All Indications**
	Medication error (reconstitution with lidocaine*)*
	Bladder Disorder Indications
	Pyelonephritis in patients with bladder disorders with urinary incontinence

II.B Summary of Important Risks

Important Identified Risk: Pre-existing Neuromuscular Disorders	
Evidence for linking the risk to the medicine	Global Safety Database and literature

Risk factors and risk groups	Patients with known or unrecognized neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise with the use of typical doses of BOTOX®.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: BOTOX® and VISTABEL® SmPC section 4.4, where advice is provided for close supervision of patients Routine risk minimisation activities recommending specific clinical measures to address the risk: BOTOX® and VISTABEL® PL section 2, where advice is given for patients Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Identified Risk: Immunogenicity, Drug Resistance, and Antibody Formation	
Evidence for linking the risk to the medicine	Global Safety Database and literature; analysis of clinical trial subjects
Risk factors and risk groups	The critical factors for neutralising antibody formation have not been well characterised. Some studies suggest that BOTOX® injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation (Jankovic, 2006; Klein, 2002).
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: Listed in of the BOTOX® and VISTABEL® SmPC sections 4.3 and 4.4 Listed in of the BOTOX® and VISTABEL® PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: - SmPC recommendation to analyse the formation of toxin-neutralising antibodies in case of treatment failure - SmPC: recommendation not to exceed the dosages and frequencies of drug administration due to formation of neutralising antibodies. Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Identified Risk: Distant Spread of Toxin	
Evidence for linking the risk to the medicine	Global Safety Database and literature
Risk factors and risk groups	High doses in excess of labelled recommendations
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: BOTOX® and VISTABEL® SmPC section 4.4,

	BOTOX® PL section 2, and in the VISTABEL® PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: - SmPC: recommendation not to exceed the dosages and frequencies of drug administration due to potential of distant spread of toxins Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Identified Risk: Dysphagia in Cervical Dystonia	
Evidence for linking the risk to the medicine	Clinical trials data, Global Safety Database, and literature
Risk factors and risk groups	Patients with underlying disorders that predispose them to dysphagia (eg, JCP, individuals with pre-existing dysphagia, anatomical strictures and narrowing of the oesophagus, musculoskeletal pathologies secondary to injury, genetics, trauma) Patients with cervical dystonia Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle. Patients treated with higher than recommended doses
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: BOTOX® PL section 2 BOTOX® SmPC sections 4.4 and 4.8 BOTOX® PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for dose limiting in patients with risk of dysphagia is included in the BOTOX® SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Identified Risk: Dysphagia in Chronic Migraine patients	
Evidence for linking the risk to the medicine	Clinical trials data, Global Safety Database, and literature
Risk factors and risk groups	Patients with underlying disorders that predispose them to dysphagia (eg, individuals with pre-existing dysphagia, anatomical strictures and narrowing of the oesophagus) Patients treated with higher than recommended doses
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication:

	BOTOX® SmPC section 4.8 BOTOX® PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for dose limiting in patients with risk of dysphagia is included in the BOTOX® SmPC section 4.2 Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Potential Risk: Medication Error (Reconstitution With Lidocaine)	
Evidence for linking the risk to the medicine	Global Safety Database and literature
Risk factors and risk groups	Evidence derived from the Global Safety Database indicate that reconstitution with the wrong substance has been reported as medication error.
Risk minimisation measures	Routine risk minimisation measures: BOTOX® SmPC section 4.2 and the VISTABEL® SmPC section 6.6 includes advice for informing patients of the risk Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Potential Risk: Pyelonephritis in Patients With Bladder Disorders With Urinary Incontinence	
Evidence for linking the risk to the medicine	Neurogenic Detrusor Overactivity: clinical trials data and literature Overactive Bladder: clinical trials data and literature
Risk factors and risk groups	Neurogenic Detrusor Overactivity: Persistent vesico-ureteral reflux and recent urologic instrumentation are risk factors for pyelonephritis in patients with neurogenic bladder; ureteric obstruction (ie, stones in the ureter) Overactive Bladder: Recent UTI and diabetes
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for prophylactic antibiotics is included in the BOTOX® SmPC section 4.2 and in the BOTOX® PL section 2. Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BOTOX®.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no other studies required for BOTOX®.

Summary of Risk Management Plan for VISTABEL®

This is a summary of the RMP for VISTABEL®. The RMP details important risks of VISTABEL®, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information). The SmPC for VISTABEL® and its PL give essential information to healthcare professionals and patients on how VISTABEL® should be used. Important new concerns or changes to the current ones will be included in updates of VISTABEL®'s RMP.

I. The Medicine and What it Is Used For

VISTABEL® is authorised for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines) and/or, moderate to severe lateral canthal lines (CFL) seen at maximum smile and/or moderate to

severe FHL seen at maximum eyebrow elevation when the severity of the facial lines has an important psychological impact in adult patients (see SmPC for the full indications). VISTABEL® contains *Clostridium botulinum* type A neurotoxin as the active substance and it is given by injection.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of VISTABEL®, together with measures to minimise such risks and the proposed studies for learning more about the risks of VISTABEL®, are outlined below:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of VISTABEL® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VISTABEL®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Important identified risks	**All Indications**
	Pre-existing neuromuscular disorders
	Immunogenicity, drug resistance, and antibody formation
	Distant spread of toxin
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Important Identified Risk: Pre-existing Neuromuscular Disorders	
Evidence for linking the risk to the medicine	Global Safety Database and literature
Risk factors and risk groups	Patients with known or unrecognized neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise with the use of typical doses of BOTOX®.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4, where advice is provided for close supervision of patients PL section 2, where advice is given for patients Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Identified Risk: Immunogenicity, Drug Resistance, and Antibody Formation	
Evidence for linking the risk to the medicine	Global Safety Database and literature; analysis of clinical trial subjects
Risk factors and risk groups	The critical factors for neutralising antibody formation have not been well characterised. Some studies suggest that BOTOX® injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation (Jankovic, 2006; Klein, 2002).
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: Listed in the SmPC sections 4.3 and 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: - SmPC recommendation to analyse the formation of toxin-neutralising antibodies in case of treatment failure - SmPC: recommendation not to exceed the dosages and frequencies of drug administration due to formation of neutralising antibodies. Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

Important Identified Risk: Distant Spread of Toxin	
Evidence for linking the risk to the medicine	Global Safety Database and literature
Risk factors and risk groups	High doses in excess of labelled recommendations
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: SmPC section 4.4 BOTOX® PL sections 2, VISTABEL® PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC: recommendation not to exceed the dosages and frequencies of drug administration due to potential of distant spread of toxins Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of VISTABEL®.

II.C.2 Other Studies in Post-authorisation Development Plan

Study 191622-146 (CMO-EPI-FAS-0518) - Phase 4, multicenter, prospective, observational post-authorization safety study of VISTABEL® for the treatment of Crow's Feet Lines.

- Purpose of the study: To collect and assess the long-term safety profile of VISTABEL® for treatment of crow's feet lines