EU Risk Management Plan for

Tuzulby 20-30-40 mg prolonged -release chewable tablets

(methylphenidate hydrochloride)

RMP version to be assessed as part of this application:

RMP version number: 1.0

Data lock point for this RMP: 31 July 2024

Date of final sign-off: 12 December 2024

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical classification
CNS	Central Nervous System
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – human
GVP	Good Pharmacovigilance Practices
INN	International Non-proprietary Names
MAH	Marketing Authorisation Holder
PIL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

ADDITIONAL CLARIFICATION

The report follows the general format and content described in the Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems Rev. 2 (31 March 2017) and the Guidance on the format of the Risk Management Plan (RMP) in the European Union (EU) – in integrated format Rev.2.0.1 (31 October 2018).

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Methylphenidate hydrochloride.
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: psychostimulants. ATC: NO6BAO4.
Marketing Authorisation Applicant	Neuraxpharm Pharmaceuticals, S.L.
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Tuzulby 20 mg prolonged-release chewable tablets Tuzulby 30 mg prolonged-release chewable tablets Tuzulby 40 mg prolonged-release chewable tablets
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/0005975)
Brief description of the product	Chemical class Methylphenidate hydrochloride belongs to the pharmacotherapeutic group: psychostimulants, agents used for Attention Deficit Hyperactivity Disorder (ADHD), and nootropics, centrally acting sympathomimetics. Methylphenidate hydrochloride is a Central Nervous System (CNS) stimulant (psychostimulant) with more pronounced effects on central than on motor activities.
	Summary of mode of action The mechanism of action in humans is not fully understood; however, it is thought that the effect is due to inhibition of dopamine reuptake in the striatum without triggering a release of dopamine. The mechanism by which methylphenidate hydrochloride produces the cognitive and behavioural effects has not been clearly established.
	Important information about its composition None.
Hyperlink to the Product Information	Please refer to the product information text in module 1.3.1.
Indication(s) in the EEA	Current: Methylphenidate hydrochloride is indicated as part of a comprehensive treatment programme for ADHD in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders.

	Proposed: Not applicable.
Dosage in the EEA	Current: **Dose titration** Careful dose titration is necessary at the start of treatment with methylphenidate hydrochloride. Dose titration should be started at the lowest possible dose. **Treatment of hyperkinetic disorders/ADHD in children and adolescent (6 years and above)** For patients 6 years and above, the recommended starting dose is 20 mg given orally once daily in the morning. The dose may be titrated up or down weekly in increments of 10 mg, 15 mg or 20 mg. The 10 mg and 15 mg doses can each be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively. The dose should be individualized according to the treatment needs and responses of the patient. Daily doses above 60 mg have not been studied and are not recommended. **Long term (more than 12 months) use in children and adolescents** The safety and efficacy of long-term use of methylphenidate hydrochloride has not been systematically evaluated in controlled trials. Methylphenidate hydrochloride treatment should not and need not, be indefinite. Methylphenidate hydrochloride treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate hydrochloride for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate hydrochloride is de-challenged at least once yearly to assess the child's condition (preferable during school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued. **Switching from immediate-release to extended release** Methylphenidate hydrochloride extended-release administered as a single dose, provides comparable overall exposure of methylphenidate hydrochloride compared to the same total dose of the immediate release formulation administered twice daily. The recommended dose of Tuzulby should be equal to the total daily dose of the immediate-release formulation not exceeding a total dose of 60 mg. Examples are provided in the Table below.

<table>
<tr><td></td><td>
<table>
<tr><th>Immediate-release Methylphenidate hydrochloride dose</th><th>Extended-release Methylphenidate hydrochloride dose</th></tr>
<tr><td>10 mg methylphenidate hydrochloride twice daily</td><td>20 mg once daily</td></tr>
<tr><td>15 mg methylphenidate hydrochloride twice daily</td><td>30 mg once daily</td></tr>
<tr><td>20 mg methylphenidate hydrochloride twice daily</td><td>40 mg once daily</td></tr>
<tr><td>30 mg methylphenidate hydrochloride twice daily</td><td>60 mg once daily</td></tr>
</table>
</td></tr>
<tr><td></td><td>Proposed:
Not applicable.</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>Current:
Prolonged-release chewable tablets, each tablet contains 20, 30 or 40 mg of methylphenidate hydrochloride respectively.</td></tr>
<tr><td>Proposed:
Not applicable.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No.</td></tr>
</table>

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable since this module is not required for hybrid type of application.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable since this module is not required for hybrid type of application.

Part II: Module SIII - Clinical trial exposure

Not applicable since this module is not required for hybrid type of application.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable since this module is not required for hybrid type of application.

Part II: Module SV - Post-authorisation experience

Not applicable since this module is not required for hybrid type of application.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable since this module is not required for hybrid type of application.

Part II: Module SVII - Identified and potential risks

Not applicable since this module is not required for hybrid type of application.

Part II: Module SVIII - Summary of the safety concerns

List of safety concerns aligned with the list of safety concerns published by the Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh) after the assessment of the PSUSA on Methylphenidate hydrochloride (PSUSA/00002024/202110).

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Serious cardiovascular events • Psychosis/Mania • Verbal or motoric tics • Depression • Aggression • Drug abuse/Drug dependence • Withdrawal syndrome • Reduced weight gain* • Decreased rate of growth* • Seizures • Cerebrovascular disorders • Neonatal toxicity**
Important potential risks	• Suicidality • Sexual Maturation delayed*
Missing information	• Long-term effects

* Only relevant for products with paediatric indications.

** Only relevant for products with adult indications.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted for the products included in this RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted to assess the effectiveness of risk minimisation measures.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No planned or on-going post-authorisation efficacy studies have been imposed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Not applicable.

V.2 Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of Risk Minimisation Measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for Tuzulby (methylphenidate hydrochloride)

This is a summary of the Risk Management Plan (RMP) for Tuzulby. The RMP details important risks of Tuzulby, how these risks can be minimised, and how more information will be obtained about Tuzulby. The RMP details important risks of Tuzulby's risks and uncertainties (missing information).

Tuzulby's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tuzulby should be used.

This summary of the RMP for Tuzulby should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tuzulby's RMP.

I. The medicine and what it is used for

Tuzulby is authorised as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient (see SmPC for the full indication). Tuzulby products contain methylphenidate hydrochloride as the active substance and they are given by oral route of administration.

Further information about the evaluation of Tuzulby's benefits can be found in Tuzulby's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *<link to the EPAR summary landing page>*

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Tuzulby, together with measures to minimise such risks and the proposed studies for learning more about Tuzulby's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet 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 (e.g. 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***.

If important information that may affect the safe use of Tuzulby is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Tuzulby are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Tuzulby. 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 (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Serious cardiovascular events • Psychosis/Mania • Verbal or motoric tics • Depression • Aggression • Drug abuse/Drug dependence • Withdrawal syndrome • Reduced weight gain* • Decreased rate of growth* • Seizures • Cerebrovascular Disorders • Neonatal toxicity**
Important potential risks	• Suicidality • Sexual Maturation delayed*
Missing information	• Long-term effects

* Only relevant for products with paediatric indications.
** Only relevant for products with adult indications.

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

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 Tuzulby.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Tuzulby.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 – Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 – Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Not applicable.