LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Alvedon
(paracetamol)

Asp no: 2021-0358

This module reflects the scientific discussion for the approval of Alvedon. The procedure was finalised on 2022-12-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Alvedon, 24 mg/ml, Oral suspension.

The active substance is paracetamol. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension (new pharmaceutical form), of the previously authorised Alvedon products marketed by GlaxoSmithKline Consumer Healthcare ApS, out of which the first was authorised in 1958. Please note that a Public Assessment Report is not available for the previously authorised products.

The application for Alvedon, 24 mg/ml, oral suspension, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, GlaxoSmithKline Consumer Healthcare ApS, applies for a marketing authorisation in Sweden through a National Procedure.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology, Pharmacokinetics, Toxicology
The non-clinical overview has been written by Goffin Laurence, PhD, Glaxo Smith Kline Consumer Health and dated on 31 Jan 2020. The report refers 142 publications up to year 2019 and contains adequate non-clinical pharmacology, pharmacokinetic, and toxicology data of paracetamol. This is considered sufficient. No new studies were provided, and none are required. Alvedon, Oral suspension, 24 mg/ml is approvable from a non-clinical view.

Environmental Risk Assessment (ERA)
The applicant has provided sufficient justification to show that no significant increase in environmental exposure is to be expected from the intended registration of Alvedon, Oral suspension, 24 mg/ml. It is agreed that no significant increase in environmental exposure to paracetamol is likely by introducing Alvedon, Oral suspension, 24 mg/ml to the market and no further ERA is required.

IV. CLINICAL ASPECTS

Pharmacokinetics
The applicant has submitted three bioequivalence studies. Only one of the study, study 215262, was performed with the final formulation and is described below.

Pharmacokinetic properties of the active substance
Absorption: Following an oral dose of paracetamol maximal plasma concentrations occur at approximately 0.5-1 hours.

Elimination: The terminal half-life is 2 hours.

Study 215262
Methods
This was a single-dose, two-way crossover study conducted in 35 healthy volunteers, comparing Paracetamol suspension, 24 mg/ml, oral suspension with Panadol B&I, 24 mg/ml, oral suspension under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours post-dose. Plasma concentrations of paracetamol were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2021-08-23 and 2021-09-08.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for paracetamol, n=35.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**47.18 ± 9.37**	**11.63 ± 2.26**	**1.00 (0.33-4.00)**
Comparator	**48.12 ± 10.75**	**11.59 ± 2.49**	**1.00 (0.50-2.00)**
***Ratio (90% CI)**	**98.69 (96.46-100.97)**	**100.73 (95.63-106.10)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90 % confidence interval for the ratio of the test product and comparator fell within the conventional acceptance range of 80.00-125.00 %. Comparable median and range was shown for t_{max}. T_{max} of 4.00 hour was only shown for one subject. When this subject is excluded, the t_{max} range for the test product is 0.33-2.00 hours.

Discussion and overall conclusion
It is acceptable to use Panodil oral suspension (described as Panadol B&I in the study report submitted by the applicant) as comparator in this extension application as the product is included in the same Global Marketing Authorisation as Alvedon products. Thus, bridging to the approved formulation of Panodil oral suspension is an acceptable approach.

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and Paracetamol oral use immediate release formulations product-specific bioequivalence guidance (EMA/CHMP/356877/2017). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Paracetamol Paediatric Suspension is considered bioequivalent with Panadol B&I.

Pharmacodynamics
No new PD data on Alvedon oral suspension 24 mg/ml were submitted.

While treatment with paracetamol is well established, its mode of action is not fully understood. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), whose analgesic and anti-inflammatory effects are thought to relate to their inhibition of the cyclooxygenase enzymes (COX-1 and COX-2), paracetamol is a weak anti-inflammatory agent with an absence of COX-related adverse effects. It has been suggested that paracetamol may exert its analgesic effect via molecular targets distinct from COX which may include the effects of both the peripheral (COX inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway, cannabinoid system) antinociception processes and “redox” mechanism.

The PD characteristics of paracetamol are considered as adequately addressed in the clinical overview.

Clinical efficacy
No new efficacy data have been generated for Alvedon oral suspension 24 mg/ml (Panadol Pediatric Suspension). Paracetamol is widely used as an analgesic for the relief of mild to moderate pain and as an antipyretic agent.

The clinical efficacy of paracetamol in adults and paediatric population is well-known and the efficacy of paracemaol is considered as adequately addressed in the clinical overview.

The revised indication for Alvedon 24 mg/ml oral suspension is:

Huvudvärk, tandvärk, feber vid förkylningssjukdomar, menstruationssmärtor, muskel- och ledvärk, som analgetikum vid reumatiska smärtor, hyperpyrexi.

This indication is considered acceptable and is in accordance with the indication text in section 4.1 of the SmPC for Alvedon 24 mg/ml oral solution or the comparator Panodil 24 mg/ml oral suspension in the Swedish market.

The initially proposed dosing of Alvedon 24 mg/ml oral suspension in paediatric population in section 4.2 of the SmPC included infants from 1 months (4 kg). This age- and weight range as well as the proposed dosing volumes, which is not in line with the posology for Alvedon 24 mg/ml oral solution, which covers children from 3 months (5 kg). Therefore, this posology was consided unacceptable. The

applicant has, however, harmonised to the dosing recommendations in children of Alvedon 24 mg/ml oral suspension with the approved posology of Alvedon 24 mg/ml oral solution. The revised dosing recommendations in children in section 4.2 of the SmPC include children from 3 months (5 kg) up to 12 years (40 kg). This is accepted.

Clinical safety
This application is based on essential similarity with Alvedon 24 mg/ml and Panodil 24 mg/ml oral suspension and as a consequence no new safety studies have been conducted with Alvedon 24 mg/ml oral suspension. There are no post-marketing data available for Alvedon 24 mg/ml oral suspension (PANADOL Pediatric Suspension).

The overall safety profile of paracetamol is well known with extensive safety monitoring conducted on all currently marketed formulations. The applicant has summarised safety data of paracetamol use from post-marketing setting, including literature references exploring the use of paracetamol by children and infants in a number of clinical settings. A total of 17114 (45%) cases met the criteria for a serious adverse event (including overdose cases). Most events were reported within the following 4 SOCs: skin and subcutaneous tissue disorders (13235), injury poisoning and procedural complications (12013), general disorders and administration site conditions (10604), and gastrointestinal disorders (8250).

The reported adverse events were considered to be aligned with the known safety profile of paracetamol or were suggested to be symptoms of the underlying condition being treated. The risk of hepatotoxicity following accidental or intentional overdose is considered a known important identified risk in adults as well as in children. Further, the safety profile of paracetamol (up to 15 mg/kg) in children has been summarized in metanalysis by Meremikwu et al., (2002) who compared efficacy and safety of paracetamol for the treatment of fever in children. Analysis of a limited number of trials (n=3) involving a total of 254 participants showed that the incidence of adverse events in the paracetamol (9/130) and placebo (4/124) groups did not differ significantly (RR 1.84, 95 % CI 0.65 to 5.18). The reported adverse events were rather mild and included drowsiness and gastrointestinal symptoms. Overall, the safety aspects of paracetamol are considered sufficiently addressed in the clinical overview.

Risk Management Plan
The submitted risk management plan is in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Avedon oral suspension 24 mg/ml.

Safety specification
Summary table of safety concerns in RMP version 0.2 (signed 02 May 2022) as proposed by the applicant in part II (Module SVIII, table 3):

Important identified risks	Hepatotoxicity due to overdose (intentional and unintentional)
Important potential risks	None
Missing information	None

The safety profile of paracetamol is considered well characterised, there are no additional pharmacovigilance activities or additional risk minimisation measures, and no specific clinical measures to address the risks identified. Paracetamol is not only presented in products with prescription status, but it is also since long widely available in OTC products for oral or rectal administration, where some of these products are obtainable even outside pharmacies.

The applicant considers that the important identified risk of ‘Hepatotoxicity due to overdose (intentional and unintentional)’ should be kept in the summary of safety concerns in the RMP. The applicant considers that this safety concern fulfils the criteria of an important identified risk as defined in GVP module V (rev 2) since e.g., potential harm from overdose whether intentional or accidental is included

in GVP Module V as a specific situation of particular interest and states that important risks following overdose should be included as a safety concern and appropriate risk minimisation measures proposed. Further, there are specific routine risk minimisation measures in place, which is beyond the product information, such as educational initiative to highlight key safety message on product websites to specifically address the risk of overdose. Messages included on product website are in line with the approved product information serves as an additional source for consumers to help them understand and minimise the risk of overdose. Also, this risk is described as an important identified risk in other RMPs for combination products containing paracetamol which have been approved by other national authorities in EU under different procedures. Moreover, it is agreed that the concern of hepatotoxicity due to overdose is maintained in recent RMP updates of paracetamol containing products (e.g., NL/H/5013/001/DC, 2021). Therefore, this concern could be retained in the summary of safety concerns.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2, signed 02 May 2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Alvedon Novum 500 mg film-coated tablets (dnr: 5.4.1-2019-44121). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the submitted data and the Applicant’s response to the questions raised on quality and clinical aspects, the present application for Alvedon 24 mg/ml oral suspension is considered approvable. Since there are no outstanding clinical issues, the overall benefit/risk balance is positive. The product information is acceptable. Therefore, the present national application for

Alvedon 24 mg/ml oral suspension is approvable provided that the applicant commits to perform a number of commitments as outlined here.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
The applicant has agreed that in q1 2023 at the latest submit an in-vitro dissolution profile study on recent batches of the test and reference product and the corresponding data, along with the equivalency of the tested batch with the batch used in the bioequivalence study.	Q1 2023

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Alvedon, 24 mg/ml, oral suspension was approved in the national procedure on 2022-12-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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