29 November 2013
EMA/18511/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Para-aminosalicylic acid Lucane

International non-proprietary name: para-aminosalicylic acid

Procedure No.: EMEA/H/C/002709

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

aNDA	abbreviated new drug application
Affsaps	Agence Française de Sécurité Sanitaire et des Produits de Santé
ATU	Autorisation Temporaire d'Utilisation
AUC	area under the serum concentration-time curve
Cmax	maximum serum concentration
DOT	directly observed therapy
DST	drug sensitivity testing
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
g	gram
GI	gastrointestinal
HIV	human immunodeficiency virus
h	hour
IZN	isoniazid
kg	kilogram
MAA	Marketing Authorisation Application
MCC	Medicines Control Council
MDR-TB	multi-drug-resistant tuberculosis
mg	milligram
MIC	minimum inhibitory concentration
mL	millilitre
M. tuberculosis	*Mycobacterium tuberculosis*
PAS	para-aminosalicylic acid
PAS Ca	calcium PAS
PAS-GR	PAS gastro-resistant granules
PAS K	potassium PAS
PAS Na	sodium PAS
PD	pharmacodynamic
PK	pharmacokinetic
TB	tuberculosis
SPC	Summary of Product Characteristics
STP	streptomycin
t½	elimination half-life
Tmax	time to maximum serum concentration
µg	microgram
US	United States
WHO	World Health Organisation
XDR-TB	Extensively-drug-resistant tuberculosis

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lucane Pharma submitted on 1 March 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for PAS-GR, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 February 2012.

PAS-GR was designated as an orphan medicinal product EU/3/10/826 on 17 December 2010. PAS-GR was designated as an orphan medicinal product in the following indication: "Treatment of tuberculosis".

The applicant applied for the following indication:

"PAS-GR is indicated for the treatment of tuberculosis in combination with other active agents. It is most commonly used in patients with Multi-Drug Resistant TB (MDR-TB) or in situations when primary medication therapy with recommended agents is not possible due to a combination of resistance and/or intolerance.

PAS-GR is indicated in adults, infants, children and adolescents."

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Para-aminosalicylic acid Lucane as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogations from market exclusivity

Not applicable

New active Substance status

The applicant did not request that the active substance para-aminosalicylic acid contained in the above medicinal product to be considered as a new active substance in itself.

Protocol Assistance

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

PAS-GR has been given a Marketing Authorisation in USA, Russia and South-Africa on 30-06-1994, 15-10-2007 and 05-08-2011 respectively.

1.2. Manufacturers

Manufacturer responsible for batch release

Laboratoires Sciencex
1 rue Edmond Guillout
F-75015 Paris
France

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Greg Markey	Co-Rapporteur:	Pierre Demolis

- The application was received by the EMA on 1 March 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2012.
- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 January 2013.
- The summary report of the inspection carried out at The Coating Place, Inc between 15 and 17 October 2012 was issued.

- The summary report of the inspection carried out at Future PAK Ltd between 18 and 19 October 2012 was issued.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 March 2013.
- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the CHMP List of Outstanding Issues on 28 August 2013.
- During the CHMP meeting on 19 September 2013, the CHMP agreed on a 2nd CHMP List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 18 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd CHMP List of Outstanding Issues on 30 October 2013.
- During the meeting on 21 November 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to PAS-GR.
- A revised opinion was adopted by the CHMP on 29 November 2013 in order to adjust the product name throughout all documents and to update statements on dosage /administration (SmPC 4.2) for the paediatric population.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application is for PAS-GR a gastro-resistant granule formulation of para-aminosalicylic acid intended for the treatment of tuberculosis (TB) in combination with other medicinal products.

The proposed indication for PAS-GR is the treatment of tuberculosis in combination with other active agents. It is most commonly used in patients (adults and children) with Multi-Drug Resistant TB (MDR-TB) or in situations when primary medication therapy with recommended agents is not possible due to a combination of resistance and/or intolerance.

The proposed posology is 4g (one sachet) three times a day i.e. every 8 hours in adults and 150 mg/kg, divided in two intakes daily for children

Tuberculosis

TB is one of the leading causes of death due to a single pathogen worldwide. It is estimated by the World Health Organization (WHO) that 32% of the world population is infected with *Mycobacterium tuberculosis.* 9.2 million new cases of TB and 1.7 million deaths from TB were reported in 2007.

Multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB)

Resistance to TB drugs is defined as a level of resistance to four times or greater the standard concentration of drug required to inhibit a fully susceptible organism. Resistance can be to a single drug, for example mono-resistance to isoniazid, or to multiple drugs, for example to both isoniazid and streptomycin.

Multi-drug resistant TB (MDR-TB) is defined as high-level resistance to both rifampicin and isoniazid with or without additional drug resistances.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDRTB with additional resistance to a fluoroquinolone and at least one second line injectable agent.

In 2006, WHO estimated that there were approximately 500,000 cases of Multi-drug resistant TB (MDR-TB). In addition, new cases of extensively drug-resistant tuberculosis (XDR-TB) have been reported around the globe.[1] This situation poses a serious problem for low income countries, especially those with a high prevalence of human immunodeficiency virus type 1 (HIV-1) infection.

MDR-TB and XDR-TB are also now of special concern in wealthy countries as a result of mass immigration giving MDR-TB and XDR-TB a high priority in global public health and biomedical research.[2]

[1] Sotgiu G, Ferrara G, Mateelli A, Richardson M D, Centis R, Ruesch-Gerdes S, Toungoussova O, Zellweger J-P, Spanevello A, Cirillo D, Lange C and Migliori G B. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. Eur Respir J. 2009; 33: 871-881

[2] Kruijshaar M E, Watson J M, Drobniewski F, Anderson C, Brown T J, Magee J G, Smith E G, Story A, Abubakar I. Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ. 2008 May 31; 336 (7655): 1231-4

In Europe, data from 2008 indicate that MDR-TB was 6.0% of the total case load for 25 countries with reporting data. Furthermore, XDR-TB reporting has increased since 2007 and 7.3% of the MDR TB cases reported from 13 countries. Therefore, MDR-TB remains a threat and XDR-TB is now established within the EU/EEA borders.[3]

Management options

The WHO guidelines on the treatment of MDR-TB proposes grouping of anti-tuberculosis agents into the following categories:

Group 1 – First-line oral agents: pyrazinamide; ethambutol; rifabutin

Group 2 – Injectable agents: kanamycin; amikacin; capreomycin; streptomycin

Group 3 – Fluoroquinolones: levofloxacin; moxifloxacin; gatifloxacin; ofloxacin

Group 4 – Oral bacteriostatic: ethionamide; protionamide; cycloserine; terizidone; para-aminosalicylic acid

Group 5 – Agents with unclear efficacy: clofazimine; linezolid; amoxicillin/clavulanate; thioacetazone; clarithromycin; imipenem/cilastatin; high-dose isoniazid.

The revised guidelines (2011)[4] state that streptomycin is considered as a first line agent and its use in MDR-TB patients is not recommended. In Group 4 products, among the oral bacteriostatic agents, the association with cure was higher with ethionamide than with cycloserine, which was higher than with PAS. Ethionamide or prothionamide should therefore always be included in a regimen unless there is a particular contraindication. PAS is recommended only if an additional medicinal product is needed to achieve a five-drug regimen or if ethionamide or cycloserine cannot be used or are unlikely to be effective.

Para-aminosalicylic acid is included in the British Thoracic Society Guidelines list of reserve drug products for MDR-TB. It recommends that treatment should start with five or more drug products to which the organism is, or is likely to be, susceptible and continued until sputum cultures become negative.

None of the agents classified in Group 4 are licensed throughout the EU. Cycloserine and ethionamide have national authorisations in a limited number of countries.

2.1.2. About the product

The product, Para-aminosalicylic acid Lucane (PAS-GR), is a gastro-resistant granular form of para-aminosalicylic acid (PAS) and belongs to the pharmacological class of anti-tuberculosis agents. It is intended to treat tuberculosis (TB) resistant to both isoniazid and rifampicin, termed multi-drug resistant TB (MDR-TB) and MDR-TB also resistant to a fluoroquinolone and a second-line injectable agent termed extensively-drug resistant TB (XDR-TB), in combination with other agents to which the bacterial organism is sensitive (WHO 2008). The intended indication is in combination with other active agents for the treatment of MDR-TB.

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[3] World Health Organization. Global tuberculosis control: a short update to the 2009 report. Geneva, Switzerland: World Health Organization; 2009.

[4] World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update. Geneva, Switzerland: World Health Organization; 2011. Available at http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf

Para-aminosalicylic acid

Para-aminosalicylic acid was the second medicinal product to be introduced for the treatment of TB in 1946. The recognition of its therapeutic role, in particular the ability to reduce the emergence of resistance to both streptomycin and isoniazid led to its use in combination with these agents in standard therapy of TB in the1940s until the 1970s. With the introduction of rifampicin and ethambutol in the 1970s and the decline in incidence of TB the use of PAS declined and standard regimens excluding PAS became routine practice throughout Europe and the United States.

In the 1950s and 1960s many products containing PAS were available and licensed and marketed for the treatment of TB in Europe, some are listed below but are no longer available:

- Spain: Apir Pas (IBYS), B-Pas (Wander), Gamirpas (Gamir), Parispas (Parisis), Vadrine (Inibsa),
- Italy: Eupasal Sodico (Sholl), Italpas Sodico (Issolabi), Pasdrazide (Bruco), Salf-Pas (Salf),
- Sweden : Na-PAS (Ferrosan),
- UK: Paramisan Sodium (Smith and Nephew), Paskalium (Glenwood), Therapas (Smith and Nephew).
- France: B-P.A.S (Laboratoires Wander), P.A.S Sodique, (Laboratoires Diamant), Para-amino-salicylate de sodium (Rhone Poulenc).

In the 1990s, TB strains resistant to the routine treatments of TB emerged and the incidences of MDR-TB and XDR-TB increased and became an obvious public health problem. The need for additional medicinal products became urgent. PAS was made available in some countries (notably the US) and from there in other countries (FR, Latvia, Portugal, amongst others).

Following the emergence of MDR-TB, PAS-GR (the formulation under consideration in this application) was developed in the USA for the treatment of MDR-TB. This gastro-resistant formulation of para-aminosalicylic acid (registered as Paser) was granted an Orphan Drug Designation and Marketing Authorisation in USA in 1994. It has also been approved in Russia and Republic of South Africa. It is included in the WHO Green Light Committee programme of essential, quality-assured second-line TB drugs since 1999. MDR-TB is now recognized as a major threat to public health within the EU. PAS is listed as an essential second-line agent for the treatment of MDR- and XDR-TB in the WHO treatment guidelines. These guidelines have been adopted by the European Centre for Disease Prevention and Control (ECDC) and are followed throughout the EU.

2.1.3. Type of application and aspects on development

In accordance with Article 10a of Directive 2001/83/EC, as amended the application relies on well-established medicinal use supported by bibliographic literature. According to Article 10a of Directive 2001/83/EC, as amended it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substance of a medicinal product has been in well-established medicinal use within the Community for at least 10 years**,** with a recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

The requirements of Article 10a application are discussed below:

a) Factors which have been taken into account by the CHMP in order to establish a well-established use

- *Time over which the substance has been used*

This medicine has been used for this indication for over 10 years.

There is evidence which show that PAS has been used for more than 10 years in the European Union.

In particular, it was used in France where the Central Pharmacy of Assistance Publique Hôpitaux de Paris (AGEPS), the largest European Public Hospital, has been supplying a form of PAS for use in the majority of MDR-TB patients from before 2000 until 2009. Since October 2009, AFSSAPS (now ANSM) approved the use of Paser (PAS-GR) on a named-patient basis under a nominative "Authorisation Temporaire d'Utilisation" (ATU) for patients with MDR- and XDR-TB. In January 2011, its use was approved under a cohort ATU (no: 589293-1).

Literature references were also submitted in support of the well-established use, in particular with regards to the period 2000-2004 for the treatment of MDR-TB or XDR-TB in combination with other anti-tuberculosis drugs in Latvia (Bloss et al 2010).

- *Quantitative aspects of use of the substance*

MDR-TB and XDR-TB are extremely rare in the European Union and therefore it is difficult to provide evidence of quantitative use beyond data available from various stated sources i.e. WHO, national treatment guidelines, literature reports, testimonials of individual treating physicians, data from France under the ATU system and from importing wholesalers.

The applicant has information which shows that PAS-GR is used in France for compassionate use under the ATU scheme. As stated above, it has been approved under a cohort ATU from 2011 (no: 589293-1) and prior to this PAS-GR was used on a named-patient basis under a nominative ATU. Over the 1st quarterly period of ATU, 65 patients received PAS-GR. On 30 June 2013, a cumulative total of 203 adults MDR-TB patients had been included in the French Cohort ATU, of whom 152 were still on treatment.

In support, there is also information which shows that a hospital preparation of PAS was used in France until 2009.

Further on, the Latvian study (Bloss 2010) reports a total of 1027 pulmonary TB cases identified over a period from 1 January 2000 to 31 December 2004. Among these patients, 686 (67%) received PAS at a daily dosage of 16 g. The individual durations of treatment were not specified.

In addition, a specific analysis on patients in the European Union (EU 27) has been provided by Dr Richard Menzies, responsible person for the global worldwide analysis on "Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients", published recently (Ahuja 2012). The studies were originally included in the Individual Patient Data meta-analysis for MDR-TB conducted for the WHO (in 2010). From this larger dataset, patients treated at seven European centres were selected (Spain, the Netherlands, Latvia, Estonia, Italy, UK and France). These had treated 1504 MDR-TB patients in total, and 280 received PAS. Patients were enrolled from 1982 up to 2008, although the majority of studies- and the largest - were conducted between 2000 and 2004.

From the above and having considered the prevalence of the disease, the CHMP concluded that PAS has been significantly used in practice in the EU for MDR-TB and that the criterion of the extent of use is fulfilled.

- *The degree of scientific interest in the use of the substance (reflected in the published scientific literature)*

The inclusion of PAS for the treatment of MDR- and XDR-TB in all International and Regional guidelines together with direct evidence of usage in various European countries as reported in the scientific literature, are considered supportive to the well-established medicinal use for this serious disease. The CHMP therefore concludes that this criterion is fulfilled.

- *Coherence of scientific assessments*

The literature provides a consistent view that PAS-GR is a treatment option as part of a multiple regimen treatment in MDRTB/ XDRTB. Overall there is coherence in the literature reviewed and analysed.

Various National Treatment Guidelines and WHO guidance state the use of PAS as part of the treatment regimen for MDR-TB and counts it as an alternative or addition to others in Group 4, namely ethionamide, protionamide and cycloserine. Its availability is critical for patients who cannot tolerate other Group 4 agents or in whom the organism has developed resistance to these agents.

The CHMP therefore concludes that this criterion is fulfilled.

b) The CHMP considers that the documentation submitted by the Applicant has covered the various aspects of the safety and efficacy and includes review of the relevant literature. The documentation, both favourable and unfavourable has been communicated.

Specific evidence of efficacy and safety of the use of PAS in MDR-TB is sparse and restricted to a small number of publications describing outcomes where PAS has been used as part of the multi-drug regimen. Likewise to the other employed medicinal products, there are no controlled studies demonstrating efficacy or safety of individual therapeutic agents. The sponsor is referring to earlier studies demonstrating efficacy and safety of PAS in the treatment of TB (Dubovski 1991) together with clinical use and has discussed the relevance of these data for the use of PAS-GR in MDR-TB.

Particular attention has been paid to any missing information and the CHMP considers that adequate justifications have been provided by the applicant demonstrating that an acceptable level of safety and efficacy can be supported.

c) The applicant explained the relevance of data submitted concerning the product reviewed in the literature being different from the product intended for marketing and provided a justification to support the usage of the enteric coated formulation that constitutes controlled release.

Based on these data, the CHMP accepted that the product studied in the literature can be considered similar to the product intended for marketing.

d) It is noted that PAS has been used in the EU and, in particular, is currently available for compassionate use in France.

2.2. Quality aspects

2.2.1. Introduction

PAS-GR is presented as gastro-resistant granules containing 4 grams of para-aminosalicylic acid as the active substance. Granules are off white to light brown, approximately 1.5 mm diameter.

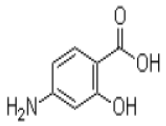
Other ingredients are: colloidal silicon dioxide, dibuthyl sebacate, methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%, hypromellose, microcrystalline cellulose and talc.

PAS-GR is available in sachets consisting of Paper/Low Density Polyethylene/Aluminium foil/Primer/Low Density Polyethylene (Paper/LDPE/alu/LDPE).

The product is supplied with a calibrated dosing spoon to measure small doses for young children.

2.2.2. Active Substance

Para-aminosalicylic acid (PAS), also known as 4-aminosalicylic acid is chemically designated as 4-amino-2-hydroxybenzoic acid and has the following structure:



This amphoteric substance appears as off white to beige powder and it is slightly soluble in water. Its solubility is increased with alkaline salts of alkali metals ($NaHC0_3$) and in weak nitric acid; the amine salts of hydrochloric acid and sulphuric acids are insoluble.

PAS has no chiral centres and therefore no stereoisomers are expected. There is possibility that the isomers (regioisomers) such as 3-amino salicylic acid, 5-amino salicylic acid and 6-amino salicylic acid may be formed. However, sufficient evidence was provided assuring that the level of these regioisomers are controlled and that the proposed manufacturing process consistently produces 4-aminosalicylic acid.

No polymorphisms have been observed for PAS. Analysis of multiple production batches by IR, melting point, and XRPD demonstrated consistency of the polymorphic form. Moreover, solvent studies showed that the same form is obtained from a variety of solvents.

Particle size of the active substance is considered a critical attribute for the manufacture of the finished product, as PAS is not dissolved in the dosage form. Therefore an appropriate test on particle size determination was included in the active substance specification.

Manufacture

PAS is synthesised by a four-step process using well defined starting materials and reagents.

Adequate in-process controls are applied during the synthesis. The specifications and control methods have been presented for the intermediate products, starting materials and reagents.

The molecular structure of PAS was elucidated by elemental analysis and spectroscopic methods. A combination of ultraviolet (UV) absorption spectroscopy, infrared (IR) absorption spectroscopy, nuclear magnetic resonance (^{1}H and ^{13}C NMR), and mass spectrometry (MS) were used to determine the chemical structure.

Potential impurities have been well discussed in relation to their origin (starting materials, manufacturing process and degradation products) and potential carry-over into the final substance. The possibility of genotoxic impurities was also considered during the development. Impurities with a potential structural alert have been identified and are controlled by appropriate specification limits.

In general, sufficient information regarding the manufacturing process, starting materials, critical steps and intermediates, process validation and manufacturing process development was provided. The synthesis and process parameters were well characterised and described.

Specification

The active substance specification includes tests for appearance, solubility, colour of solution, identity (IR, colorimetric reaction), assay (HPLC), impurities (HPLC), residual solvents (GC), pH of saturated solution, water content (KF), melting point, heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.), particle size and chlorides (Ph. Eur.).

A detailed description for all analytical methods was provided. Some of the proposed methods are in accordance with the Ph. Eur. Complete method validation data was provided for the non compendial (in-house) analytical methods.

Although the analytical method for impurity testing was considered acceptable, further improvements to this method (with regards to the sample preparation) were recommended. Currently, to prevent the degradation of one of the impurities during the analytical procedure, first dilution of the impurity reference standard is made with different diluent then dilution of the active substance whereas subsequent dilutions are performed with the same diluent. There is a risk that if the impurity is not soluble in the sample diluent, then it could not be detected in the sample. Therefore the applicant was recommended to develop, an analytical procedure where the impurity and the active substance are dissolved in the same diluent using the same preparation technique.

Furthermore, the applicant was recommended to perform the suitability test as described in Ph. Eur. 2.5.12 for the Karl Fisher (KF) method for determination of water. Very low levels of water were reported in the active substance and these were below the limit recommended by the Ph. Eur. for validation of suitability. However, the Ph. Eur 2.5.12 suitability range is given as an example only. Therefore the applicant was recommended to finalise the method validation for determination of water content in the active substance by validating the suitability range.

In general specification limits and analytical methods proposed are suitable to control the quality of the active substance.

Batch analysis results for PAS have been presented for two commercial scale batches. All batches were manufactured by the proposed commercial manufacturers according to the proposed process. Data demonstrated consistency between batches and that batches comply with the proposed specification. It can be concluded that the batch analysis results indicate that the manufacturing process is reproducible and under control.

Stability

Stability studies were not performed under ICH conditions and samples were stored at a temperature not less than 15°C which represents the long term condition.

Primary stability studies according to ICH guidelines have been initiated on three commercial scale batches of the active substance stored in the commercial package. PAS will be included in a stability program under refrigerated conditions (5°C ± 3°C). Stability data will be generated, in accordance with current ICH recommended storage conditions, to support the re-test period and storage conditions for PAS. Meanwhile, and until a re-test period is set based on suitable stability results, the active substance will be fully controlled prior to each manufacture of the finished product.

No forced degradation study was performed in support of this application. The degradation pathways were discussed based on a published literature reference. The absence of such studies was acceptable because the active substance will be fully tested before use and no-retest period was proposed.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of pharmaceutical development was to obtain a stable formulation, with high content of the active substance, in the form of spherical and smooth granules displaying uniform gastro-resistant coating to protect them from acidic degradation. The active substance is unstable at acidic conditions and has better stability in a neutral or alkaline pH range. In acidic conditions it degrades via decarboxylation and forms meta-aminophenol, the major degradation component. The formulation development was aimed at obtaining a controlled (delayed) release of the active substance able to reduce fluctuation of the plasma levels. Development of gastro-resistant dosage form was based on the fact that PAS is known for gastro-intestinal side effects and therefore the enteric coating will improve the formulation tolerability. As an age-appropriate dosage form granules also assure the flexibility to administer the product to young children by sprinkling into food or mixing with drinks.

Limited information has been provided on the development of the finished product. However the product has been commercially used in US since 1994. The applicant has provided further information based on literature references for formulation development and development of controlled release enteric coated formulation.

The finished product contains PAS formulated as microspheronised core beads that are subsequently enteric-coated. It is a delayed release formulation from the gastro-resistant coating. The excipients were selected on grounds of compatibility with the active substance and suitability for the type of wet granulation process. All excipients used in the formulation comply with the current European Pharmacopoeia monograph and are commonly used excipients for this pharmaceutical form. The wet granulation process selected was extrusion/spheronisation. For this process, shape, size and yield were considered critical quality attributes in order to produce uniform coating and to adequately control dissolution.

A summary of studies performed to optimize both the enteric coating and the controlled release coating was presented. It was shown that the use of Eudragit L-30D was found to be successful in protecting the product during the acid stage. For the controlled release in the buffer medium (phosphate buffer), a combination of ethylcellulose dispersion (Aquacoat) with hypromellose and with dibuthyl sebacate as plasticizer was found to be appropriate. The chosen release-rate controlling coating was found to be adequate to delay the dissolution of the spherical granules which could provide twice daily dosing.

Dissolution method for testing dissolution of the granules is based on two phase testing, one in the acidic medium to test for enteric coating and the second phase is for alkaline medium. Dissolution method is well designed for this type of specialized dosage form. Although the dissolution method is sensitive enough to detect batches of the finished product that do not comply with the specification, its discriminatory power has not been fully documented. However, appropriate applied in-process controls, as well as the manufacturer's experience with the product provide assurance that only batches that comply with the proposed specifications are released. Nevertheless, the applicant was recommended to continue its efforts for developing a dissolution method with an appropriate discriminatory power or to further demonstrate the discriminatory power of the currently used method.

According to SmPC, the contents of the sachet (granules) could be added to a glass of orange or tomato juice. They will not dissolve, but swirling the juice in the glass will help re-suspend the granules if they sink. A justification that the enteric coated granules will not dissolve in acidic foods has been provided. However, the pH of foods is known to fluctuate with brands. No compatibility study has been provided and the applicant has modified the instructions in the SmPC that these granules should be taken immediately after dispersion. It has been demonstrated that the enteric coating is resistant to acidic pH, and that its functionality is preserved in the acidic vehicles proposed for administration in the SmPC, therefore it should also preserve the active substance from contact with those vehicles during administration. These indicate that PAS-GR granules will be stable in any acidic fluids such as orange juice or tomato juice.

A measuring device (measuring spoon) has been developed to measure the prescribed dose when below 4 g per intake (few patients, mostly children, may need a lower daily dose usually 150 mg of PAS per kg of body weight per day, divided in 3 intakes). The device called "Spoonbox" has been designed to sample from 500 mg expressed in active substance up to 3750 mg. The increment is 250 mg. The device is CE marked. The dosing device is adapted to the posology regimen. The marking appearing on the Spoonbox (graduated scale and scale intervals) are suitable in relation to the dosing advice as stated in the SmPC.

Granules are packed in sachets consisting of Paper/Low Density Polyethylene/Aluminium foil/Primer/Low Density Polyethylene (Paper/LDPE/alu/LDPE). The container closure system complies with the Ph. Eur. and the EC requirements. The choice of the packaging has been validated by stability data and is adequate for the intended use of the product.

It can be concluded that the formulation development of the product was satisfactorily described. The key critical parameters were identified and evaluated.

Adventitious agents

No excipients derived from animal or human origin are used for the preparation of the finished product.

Manufacture of the product

Main steps of the manufacturing process of the finished product are wet mixing, extrusion, spheronisation, fluid-bed drying, sieving, coating and filling into sachets. Detailed description of the manufacturing process was provided.

The applicant has provided sufficient information on the manufacturing process of the granules and all the in-process controls that are applied during the manufacture. The manufacturing process takes place at two sites; one is responsible for the manufacture of the uncoated granules and packaging of the final product, and the other site is responsible for coating. The manufacturing process has been

validated and it was demonstrated to be capable of reproducibly producing a finished product of the intended quality. Adequate in-process controls are in place for this pharmaceutical form.

Product specification

The finished product release specification include appropriate tests for appearance, identification (HPLC, colour reaction and UV), water content (KF), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), assay (HPLC), related substances (HPLC) and microbiological purity (Ph. Eur.).

A detailed description for all analytical methods was provided. Complete method validation data was provided for the non compendial (*in-house*) analytical methods.

Batch analysis results on seven industrial batches confirm consistency and uniformity of manufacture and indicate that the process is capable of consistently producing a finished product that meets the predefined specifications and that the manufacturing process is under control.

Stability of the product

Stability data have been provided for three industrial scale batches of the finished product. The stability batches have been manufactured according to the manufacturing process proposed for marketing and the samples were packed in the container proposed for the market. Up to eighteen months stability data have been provided under long term conditions (25ºC/60%RH) according to ICH conditions. In addition results for 5 batches stored under non-ICH conditions (15ºC) were provided in support of the shelf-life. Stability data were available on 18 months for 2 batches and 12 months for 3 batches stored under 15ºC conditions. All results comply with specifications.

Samples were tested for appearance, water content, assay, related substances and dissolution. The analytical procedures used were stability indicating and these were the same analytical methods as used for release of the finished product.

The overall stability data for PAS gastro-resistant granules proved that the product is stable under tested conditions. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided about the active substance, PAS, was of acceptable quality. In general sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described. Specification limits and analytical methods are suitable to control the quality of the active substance. No re-test period for the active substance was established as stability data were not sufficient. Para-aminosalicylic acid must be tested prior to use.

Selection of the type of formulation and of the manufacturing process has been justified. Limited information has been provided on the development of the finished product and this was accepted in view of the fact that the product has been commercially used in US since 1994. The applicant has provided further information based on literature references for formulation development and development of controlled release enteric coated formulation. This is based on the fact that PAS is known for GI side effects and therefore the enteric coating will improve the formulation tolerability. The controlled release formulation is based on a publication where the authors have suggested that the use of controlled release formulation will reduce fluctuations of the active substance in plasma.

Physicochemical and biological properties of the finished product have been well analysed, and the critical parameters for performance of the product have been defined and are routinely controlled, namely acid resistance, solubility in neutral pH solutions and bead particle size.

The method of manufacture is considered standard and has been satisfactorily described, including in-process tests. The data shows consistent manufacture and is considered sufficient for this manufacturing process. A satisfactory validation protocol has been provided.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. Development of an analytical test procedure where the impurity standard and the sample (active substance) are dissolved in the same diluent using the same preparation technique. The new method, appropriate validation data, and analytical results for at least 3 consecutive production scale batches of the active substance should be implemented via appropriate regulatory procedure.
2. Validation of the method for the determination of water content in the active substance (Karl Fisher method). Linearity, accuracy, precision, and intermediate precision should be determined.
3. Development of an alternative dissolution method with an appropriate discriminatory power or demonstration that the current dissolution method has an appropriate discriminatory power to be able to differentiate between batches that meet specification requirements and batches that will be out of the specification limits.

2.3. Non-clinical aspects

2.3.1. Introduction

Since literature references have been provided in support of the application (with many studies performed more than 60 years ago until 2004), it cannot be verified whether the studies cited were in compliance with GLP regulations, however, it is assumed that the studies were conducted in compliance and accordance with the standards prevailing at the time of conduct of the studies. This is however satisfactory due to the accepted well established use of the product.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A number of *in vitro* studies have demonstrated that PAS is bacteriostatic against *M. tuberculosis*, whereby the minimum inhibitory concentrations (MIC) ranged between 1 and 10 µg/mL and anti-bacterial activity was reported in a few MDR strains.

In vivo efficacy has also been reported in mouse models of tuberculosis; the effective concentrations appear to range from 1% to 5%. Para-aminosalicylic acid is believed to exert its effect on *M. tuberculosis* via an inhibition of folic acid biosynthesis and/or inhibition of mycobactin synthesis (which in turn reduces iron uptake). However, the exact mechanism is yet to be elucidated.

Secondary pharmacodynamic studies and safety pharmacology

Safety pharmacology studies do not appear to have been conducted; however, clinical data are not indicative of a potential to cause substantial effects on the cardiovascular, respiratory or central nervous systems.

2.3.3. Pharmacokinetics

Animal studies have shown that PAS is rapidly and totally absorbed, and rapidly excreted. The distribution of PAS *in vivo* was evaluated in the rat, guinea-pig and rabbit. Repeated dose studies appear to have been performed in the rat and the data do not suggest any demonstrable retention of PAS. The majority (80-90%) of the administered dose is excreted in urine and is excreted mostly as unchanged compound.

Studies in the dog suggest that probenecid had no effect on the clearance of PAS and the applicant has suggested that clinical data are supportive of this finding. E*x vivo* studies using rat stomach and bowel suggest that PAS may interfere with the penetration of vitamin B12 across the bowel wall. In light of these findings, the potential for malabsorption of Vitamin B12 has been included within the SmPC, section 4.5.

2.3.4. Toxicology

The applicant has suggested that a review of the literature identified no general toxicity studies of PAS that were relevant to the application. Under these circumstances, non-clinical investigations are normally not required when there is sufficient well-documented clinical experience to establish all aspects of clinical efficacy and safety. No safety issues with the excipients, dibutyl sebacate and hydroxypropylmethylcellulose were identified. The applicant has indicated that the maximum repeatable dose of dibutyl sebacate in a 2-year rat study was higher than that proposed clinically; which is supportive of the use of this excipient, given that the proposed treatment duration is up to 24 months.

The genotoxic potential of PAS-Na appears to have been investigated *in vitro*. The active substance was non-mutagenic in the Ames test, but caused chromosomal aberrations in human lymphocyte cells. However, the effective concentrations were higher than that observed clinically. No *in vivo* genotoxicity studies have been performed with PAS-Na. The applicant undertakes to do so (post-authorisation).

Carcinogenicity studies have not been performed which is not surprising as this compound was marketed well in advance of the ICH S9 Guideline. The applicant has clarified that PAS has not been identified as a carcinogen and that no cases of cancer have been associated with the clinical use of PAS.

The effects of PAS-Na on embryofetal development have been evaluated in the rat and rabbit. An increase in fetal weight was noted in both the rat and rabbit. Skeletal malformations (involving the skull bones and the sternum) were noted in the rat at 77 mg/kg/day. Although these findings were not of a dose-related nature, it is evident that the exposures evaluated in the rabbit study are below those proposed clinically and so no definitive conclusions with respect to reprotoxicity can be made at this time. The applicant has proposed to use standard pharmacovigilance reporting systems to monitor the risk of PAS-GR use in pregnant women.

For the drug substance and drug product, the majority of the proposed impurity limits are in line with ICH Q3A(R2) and ICH Q3B(R2) Guidelines, and/or are acceptable from a toxicological point of view.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the Questions and answers document for the Guideline on the environmental risk assessment of medicinal products for human use [EMA/CHMP/SWP/44609/2010], Log P has been determined experimentally (shake-flask, slow-stirring or eventually HPLC method); however, the final study report should be provided.

In accordance with the EMA “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use” [CHMP/SWP/4447/00, 1 June, 2006], the applicant has refined the fraction of market penetration (Fpen) based on prevalence of the disease, and estimated that the PEC surface water will be below the threshold limit of 0.01 µg/L. Further clarification of calculations performed in order to refine the Fpen is required. In addition, the applicant has not adequately discussed the impact of the anti-microbial activity of PAS-GR on the environment. Further discussion with respect to the anti-microbial activity of PAS-GR and its potential effect on the environment is necessary.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation to be addressed:

The Phase I ERA is still considered to be incomplete and the following issues still need to be addressed:

- The applicant should ensure that the periodical consumption of PAS-GR is based upon the maximum proposed treatment duration of 24 months.
- During the calculation of CONai, it is not clear how the figure of 1100 was derived. The formula described in the Q&A (p.12/12) on Guideline on the environmental risk assessment of medicinal products for human use concerning Fpen and CONai region should be correctly applied, and the values used should be clearly justified
- In accordance with ERA guideline, for phase I, the estimation should be based only on the drug substance, irrespective of its route of administration, pharmaceutical form, metabolism and excretion. Hence the factor of 0.8 for the calculation of CON_{ai} should be deleted.
- The Phase I ERA is still considered to be incomplete as the applicant still has not adequately discussed the anti-microbial properties of PAS-GR. At the very least, an estimate of PECSW:PNECmicroorganism should be provided as PAS is considered to be a compound with anti-microbial activity that could affect microbial communities.

The applicant is advised to carefully consider the outstanding deficiencies of the ERA and if the PECsw value is equal to or above 0.01g/L; then a Phase II environmental fate and effect analysis should be performed. The applicant should commit to providing a revised ERA which addresses these concerns within 12-18 months of approval.

2.3.6. Discussion on non-clinical aspects

A number of *in vitro* studies have demonstrated that PAS is bacteriostatic against *M. tuberculosis*, whereby the minimum inhibitory concentrations (MIC) ranged between 1 and 10 µg/mL and anti-bacterial activity was reported in a few MDR strains. The data presented suggest that PAS is fairly specific for *M. tuberculosis*; however, the applicant has subsequently clarified that PAS is active against *M. bovis* at similar concentrations.

In vivo efficacy has also been reported in mouse models of tuberculosis; the effective concentrations appear to range from 1% to 5%; although, there was some discrepancy with respect to the effective *vs* the toxic concentrations.

The distribution of PAS *in vivo* was evaluated in the rat, guinea-pig and rabbit. Repeated dose studies appear to have been performed in the rat and the data did not suggest any demonstrable retention of PAS. However, the maximum study duration appears to be 48 hours. Given that the proposed treatment duration is up to 24 months, the applicant was asked to discuss the potential for retention of PAS-GR following repeated administration. In the absence of non-clinical data, the applicant has made reference to clinical data which suggests that there is some evidence of accumulation over time. However, the absence of published reports of severe adverse events (SAEs) with PAS or PAS-GR, suggests that any potential accumulation of PAS does not translate into significant toxicity.

In accordance with the SmPC Guideline (2009), the applicant was asked to clarify the level of information available as to whether PAS is a substrate, inducer or inhibitor of the enzymes and transporter systems [e.g. cytochrome P450 (CYP) enzymes, P-gp, organic anion transporters]. The data from the literature suggest that PAS-GR is unlikely to cause any clinically significant interactions

at the level of the CYP enzyme. The applicant was unable to locate data on the potential for interactions at the level of transporter systems and no further information is requested.

The non-clinical safety data in support of PAS-GR was quite limited and it is the view of the CHMP that additional general toxicity data would not be necessary in light of the availability of clinical data. The applicant has agreed to submit further safety data by way of Periodic Safety Update Reports (PSURs).

In vitro, PAS-GR was shown to be genotoxic at concentrations in excess of those proposed clinically. In accordance with the ICH S2(R1) guideline, the applicant should conduct an *in vivo* genotoxicity study and provide the data as a post-authorisation commitment. In addition, Section 5.3 of the SmPC reflects the level of information available.

The effects of PAS-Na on embryofetal development have been evaluated in the rat and rabbit. Skeletal malformations (involving the skull bones and the sternum) were noted in the rat at 77 mg/kg/day. Although the incidence of these findings was not considered to be dose-related, the proposed SmPC has been revised to reflect the observed findings and to give some indication of how the no-effect/effect doses relate to that proposed clinically.

The Phase I environmental risk assessment (ERA) is still considered to be deficient. The periodical consumption of PAS was based upon a 10 month treatment period when in clinical practice, PAS-GR may be administered for up to 24 months; so this should be rectified. The formula described in the Q&A (p.12/12) on Guideline on the environmental risk assessment of medicinal products for human use concerning Fpen and CONai region should be correctly applied, and the values used should be clearly justified. In accordance with ERA guideline, for phase I, the estimation should be based only on the drug substance, irrespective of its route of administration, pharmaceutical form, metabolism and excretion. Moreover, the applicant still has not adequately discussed any broad anti-microbial properties of PAS-GR. At the very least, an estimate of PECSW:PNECmicroorganism should be provided as PAS is considered to be a compound with anti-microbial activity that could affect microbial communities. The applicant is therefore advised to carefully consider the outstanding deficiencies of the ERA and if the PECsw value is equal to or above 0.01 µg/L; then a Phase II environmental fate and effect analysis should be performed.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers the following measures to address the non-clinical issues:

- An in vivo genotoxicity study should be conducted with PAS-GR;
- To provide a final study report for determination of the octanol:water coefficient
- To provide a revised environmental risk assessment within 12-18 months of Marketing Authorisation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

Due to the bibliographic nature of this application, it cannot be verified whether the studies cited were in compliance with GCP regulations. However, it is assumed that these were conducted in compliance and accordance with the standards prevailing at the time of conduct of the studies.

2.4.2. Pharmacokinetics

Absorption

According to the applicant the initial and pivotal PK study (Peloquin 1994) for PAS-GR was conducted in 12 adult healthy volunteers (7 women including 1 dropout, and 5 men). Following an overnight fast and the oral administration of a single 4 g dose of Paser (PAS-GR), 15 serial plasma samples and 5 consecutive urine collections were taken over a 24 hour-period. Plasma concentrations of PAS and its inactive metabolite acetyl-PAS (AcPAS) were measured by HPLC.

PAS showed a median (range) time to peak concentration of 6h (1.5 to 24h, with a single outlier female volunteer at 24h). Plasma concentrations peaked with a median (range) of 15.25µg/mL (9.36-35.4). The acetylated metabolite of PAS (Ac-PAS) peaked with median (ranges) time of 8h (4-24) and plasma concentrations of 17.61µg/mL (13.17-22.86).

The plasma half-life of PAS from PAS-GR was 1.62±0.85 h *i.e.* it was twofold higher when compared to that from earlier formulations, partially because of the prolonged absorption of the granules. The absorption profile of PAS-GR was delayed (no test) as compared with historical data.

In a similar historical study (Wan 1974a[5]), a single dose of 4 g sodium PAS (PAS Na) was administered in a fasting state either dissolved or suspended in 250 mL water in 3 out of the 12 healthy volunteers. Peak plasma levels of PAS occurred at 0.5h. Other salts of PAS were also tested in groups of 3 healthy volunteers each and showed earlier peaks than with PAS-GR: 0.75h for potassium PAS and 1.5-2 h for calcium PAS, respectively. Moreover, the absorption of the free acid was erratic with delayed peaks after 3-4 h because of poor dissolution of the free acid given as a suspension. A follow-up study from the same group (Wan 1974b[6]) confirmed most findings of the earlier study on a group of healthy volunteers participating to each of the 4 consecutive sequences (one sequence per drug).

A comparison of PK parameters of single oral doses of 3-6 g of PAS or PAS-GR in various studies performed historically and involving a total of 60 adult healthy volunteers shown that absorption of four different drug forms was essentially complete, with sodium PAS having a statistically significant ($p<0.05$) higher rate of absorption than PAS or than Ca PAS (Wan 1974a, Wan 1974b). In adult healthy volunteers receiving a single dose of 4 g of PAS-GR the typical Cmax was much lower

[5] Wan SH, Pentikainen P, Azarnoff DL: Bioavailability of aminosalicylic acid and its various salts in humans. III. Absorption from tablets. J Pharm Sci 1974 May; 63(5): 708-711

[6] Wan SH, Pentikainen P, Azarnoff DL: Bioavailability studies on para-aminosalicylic acid and its various salts in man. I. Absorption from solution and suspension. J Pharmacol & Biopharmaceut 1974; 2: 1-12

(between 3 and 7 times) than that obtained with tablets of PAS. Peak plasma concentrations were also achieved much later with a typical Tmax delayed at least twofold with granules of PAS-GR compared with tablets of PAS.

According to the applicant, the PAS-GR formulation should therefore allow a smoother rise in plasma concentrations. Moreover, its delayed absorption as compared to historical formulations of PAS should limit the occurrence of AE which were mostly related to an immediate gastric effect of these formulations.

Influence of food

The effects of food on the PK of a single dose of 6 g of Paser were evaluated under five different conditions (fasting, food, orange juice, antacids, and high-fat meal) in the Peloquin 2001 study. Subjects receiving a high-fat meal presented significantly delayed Tmax and higher Cmax when compared to fasting subjects ($p<0.05$). As expected when compared to data from previous studies with para-amino benzoic acid (Drucker 1964), both the rate and extent of absorption of PAS were affected by a high-fat meal. Statistically significant ($p<0.05$) increases in AUC0-inf by 1.7 fold and in 24h-urinary recovery by 1.5 fold were observed in the Peloquin 2001 study. An increased solubility of the free acid in the small intestine in the presence of lipids could be the cause of the increase in both the rate and extent of absorption. Following the higher amount administered as explained above, though not a direct comparison, the relative proportion of Ac-PAS in the urine was decreased from 65% with 4 g PAS-GR (Peloquin 1994) to 53% with 6 g PAS-GR (Peloquin 2001).

The changes in PK parameters were minimal with the co-administration of other “food” (either orange juice or antacids).

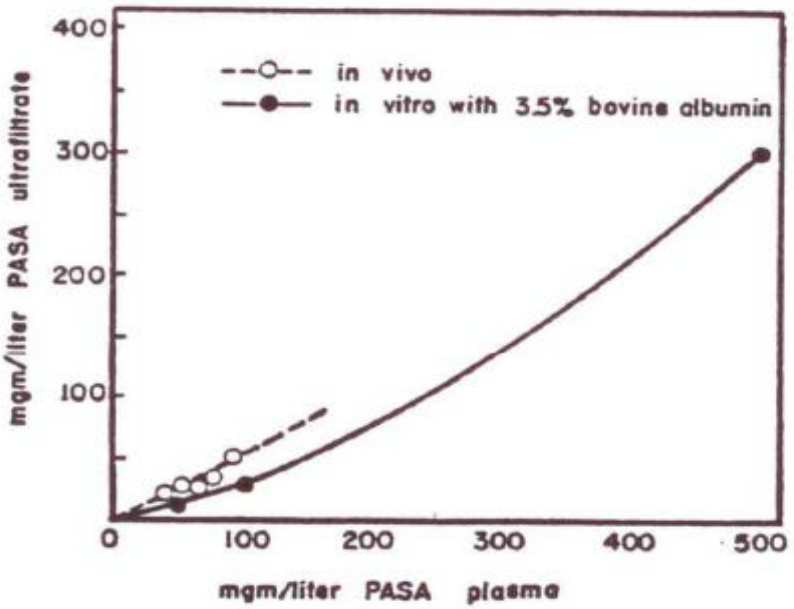
Distribution

According to the applicant the distribution of PAS has been established in historical studies, including Way 1948[7] , after a single oral dose of 4 g of sodium PAS. At 15 minutes about 70% of the compound was present in the plasma and it remained unchanged after 3 hours. *In vitro* experiments using the ultra-filtration technique with 0.05, 0.1 and 0.5 g of PAS dissolved in 3.5% BSA were used to determine the albumin binding of PAS. At plasma levels of 40-100µg/mL*, i.e.* those achieved with historical formulations, 50-60% was bound to plasma proteins, presumably albumin (Figure 1). Albumin binding decreased from 70% to 60% and 50% in an inverse relationship to the increase in PAS concentration. As concentrations achieved with PAS-GR are at least twofold lower than with these old formulations, albumin binding might not be higher with this new formulation.

[7] Way EL, Smith PK etal: The absorption, distribution, excretion and the fate of para-aminosalicylic acid. J Pharmacol Exp Ther 1948 Jul; (3): 368-382

Figure 1

Figure 3: Protein binding of PAS as a function of increasing PAS concentrations (Way 1948)



Elimination

In the Way 1948 study, nine healthy adults received a single 4 g oral dose of sodium PAS, approximately 85% of the compound was found urine within 7 hours either free or conjugated. According to the applicant, this rapid excretion of PAS suggested that to maintain clinical effectiveness it had to be given at four hour intervals. As shown in two other studies (Wan 1974a and Wan 1974b), there was no significant difference in the total amount of excreted metabolites between all forms tested. In the pivotal PK study for PAS-GR (Peloquin 1994), within 24h post-dose, the median quantity of PAS and that of Ac-PAS in the urine were approximately 260 and 2300 mg, respectively, showing that, as with historical formulations described above, most of the 4000 mg-granules dose was recovered in the urine. Therefore the coefficient of extraction (F) 65.2% represents a low estimate for F, close to the ratio obtained from AUC0-24 of PAS-GR compared with simulated AUC0-24 from other PAS formulations in patients (59.6%). The median renal clearance of PAS-GR was only 7.3% of the Cl/F ratio3, as most of it was acetylated before excretion. The estimates for Ac-PAS renal clearance were similar to the Cl/F ratio, suggesting this metabolite is primarily cleared by the kidneys.

Metabolism

The major metabolites of PAS are by conjugation: to glycine in para-aminosalicyluric acid (PASU) up to 25% of the dose and to N-acetyl in N-acetyl para-aminosalicylic acid (Ac-PAS) up to 70% of the dose. Together they constitute more than 90% of the total metabolites of PAS found in urine as demonstrated in Way 1948, Wan 1974a and Wan 1974b). In the Wan 1974a study the apparent discrepancy in the bioavailability of PAS (calculated from plasma concentrations and urinary excreted metabolites) was explained by the concentration-dependent metabolism of PAS into Ac-PAS, responding to rate limiting capacity of acetylation during absorption, as previously shown with para-amino benzoic acid (Drucker 1964). The follow-up study (Wan 1974b) confirmed the capacity-limited

formation of Ac- PAS. When the rate of absorption is high (increased drug doses, or boluses), during the absorption phase high concentrations of drug traverse the gut and perfuse the liver, saturating enzymatic acetylation capacities in the liver. Consequently, the relative proportion of acetylated metabolite in the excreted waste decreases. Conversely if the rate of absorption is low or doses are administered in repeated small intakes, concentrations of drug perfusing the liver cannot influence the metabolism and Ac-PAS is produced in proportionally larger quantities. The ratio of Ac-PAS/PAS in the urine was 2.74 for PAS acid (with absorption delayed) compared with a mean of 1.28 for the salts (Wan 1974b). Expressed as a percentage of absorbed drug excreted as Ac-PAS, there was a significantly higher ($p<0.05$) proportion of 73.1% for PAS compared with 56.4% for PAS Na, 57.7% for PAS Ca and 54.5% for PAS K. Moreover, this capacity limitation step occurs during the absorption phase and first-pass effect in the GI tract and the liver, as the rate constant for elimination was the same in all cases.

Special populations

Patients with hepatic impairment

The PK of 20 mg/kg IV-PAS administered in 3 min-boluses were compared in 7 patients with liver disease (4 alcoholic cirrhosis, 2 acute viral hepatitis, 1 chronic cholangitis) was compared with the PK obtained in 7 healthy volunteers in a study[8] by Held. The half-life and plasma clearance were within the same ranges in the 2 populations as seen in Table 1 below.

Patients with renal impairment

In the study by Held, 5 patients with terminal renal failure who were under chronic dialysis showed half-life in the same range as that in healthy volunteers, however the plasma clearance was significantly lower ($p <0.025$) in healthy volunteers, see Table 1.

Table 1

Table 6: PK parameters of PAS in patients with hepatic and renal failure (Held 1977)

Group	N	Weight (kg)	Half-life (min)	Clearance (mL/kg/min)
HV	7	75.3±4.2	26.4±5.5	2.62±0.6
Liver disease	7	72.3±6.4	27±2.5	2.56±0.43
Renal failure	5	68.2±5.1	30.8±4.7	3.28±0.59

The elimination rate of PAS depends on its metabolism and renal clearance which are both dose-dependent. However as the renal clearance of the 2 main metabolites are greater than that of PAS, the rate limiting parameter of its elimination should be liver function. However this was not confirmed in this study as the PK was not altered in patients with hepatic failure. Conversely in renal failure patients, PAS was more rapidly eliminated which was also unexpected from a product mainly eliminated unchanged by the kidney. The increased plasma clearance of PAS could be explained by an altered distribution (partly related to a decreased protein binding) of the drug and/or an increased activity of the conjugation enzymes in patients with terminal renal failure.

[8] Held H, Fried F: Elimination of para-aminosalicylic acid in patients with liver disease and renal insufficiency. Chemotherapy 1977; 23(6): 405-415

Pharmacokinetic interaction studies

Based on early studies showing prolonged half-life, plasma concentrations, urinary excretion of free fraction in rapid acetylators, and decreased albumin binding of isoniazid in the presence of PAS.[9][10]

In the studies by Palva[11] and Heinivaara[12] PAS caused decreased intestinal absorption of vitamin B12, leading to deficiencies seen during prolonged treatment of at least two weeks. The interaction could be mediated *via* competitive inhibition of the absorption of folate which is structurally similar to PAS; the production of the intrinsic factor or its binding to vitamin B12 remained normal[13][14]. According to the study by Heinivaara megaloblastic anaemia however is only extremely rarely reported and in a study in 74 patients treated with PAS for a maximum of 3 years no case was reported.

Statistically significantly decreased serum concentrations and prolonged Tmax of rifampicin (10mg/kg/d) were observed throughout the 8 hour-observation period in 30 patients concomitantly receiving oral 0.2 mg/kg/d of PAS granulates (Boman 1971). This interaction was actually related to one excipient (bentonite) in the formulation of the granules (and not in the tablets) which was shown to adsorb rifampicin rapidly and strongly (Boman 1975). The PAS-GR formulation is devoid of any bentonite.

PAS was shown to significantly interfere with the absorption of oral digoxin by reducing its plasma concentrations and AUC. It was shown however that this interference was not by adsorption with digoxin but possibly through changes in the function of the intestinal wall as shown on a severely reduced D-xylose absorption[15]

In an heterogeneous group of 5 healthy volunteers and 6 TB patients, granulated sodium PAS in a dose regimen of 3x4 g on Day1 and 10 g on Day 2 did not modify plasma levels of cycloserine (3x250 mg on Day1 and 500 mg on Day 2) as assayed in bioassays, whereas the chemical assays showed significantly ($p<0.05$) lower concentrations of cycloserine. It was hypothesized that PAS could delay the biotransformation of cycloserine therefore prolong its half-life and retard the formation of inactive metabolites of cycloserine; PAS did not modify the albumin binding of cyscloserin or its urinary elimination.[16]

In another study, commonly co-administered second line drugs were reported to have no effect on the PK of PAS-GR in healthy volunteers. However, no group receiving PAS-GR alone was available; moreover these PK data are not provided in the publication: it is only stated that very similar PK parameters were observed when PAS-GR was administered together with cycloserine, ethionamide, clofazimine and pyridoxine (Peloquin 2001) as compared to former studies without these co-administered drugs (Peloquin 1994).

[9] Mandel W, Heaton AD, Russell WF Jr, Middlebrook G: Combined drug treatment of tuberculosis. II. Studies of antimicrobially-active isoniazid and streptomycin serum levels in adult tuberculous patients. J Clin Invest 1959 Aug; 38(8):1356-1365

[10] Tiitinen H: Modification by para-aminosalicylic acid and sulfamethazine of the isoniazid inactivation in man. Scand J Respir Dis 1969; 50(4): 281-290

[11] Palva I. Vitamin B12 deficiency in fish tapeworm carriers. A clinical and laboratory study. Acta Med Scand Suppl. 1962;374:1-86

[12] Heinivaara O, Palva IP: Malabsorption and deficiency of vitamin B 12 caused by treatment with para aminosalicylic acid. Acta Med Scand 1965 Mar; 177: 337-341

[13]Palva IP, Heinivaara O, Mattila M: Drug-induced malabsorption of vitamin B 12. 3. Interference of PAS and folic acid in the absorption of vitamin B 12.Scand J Haematol. 1966; 3(2): 149-153

[14] Palva IP, Rytkönen U, Alatulkkila M, Palva HL: Drug-induced malabsorption of vitamin B 12 . V. Intestinal pH and absorption of vitamin B 12 during treatment with para-aminosalicylic acid. Scand J Haematol 1972; 9(1):5-7

[15] Brown DD, Juhl RP, Warner SL: Decreased bioavailability of digoxin due to hypocholesterolaemic interventions. Circulation 1978 Jul; 58(1):164-172

[16] Mattila MJ, Nieminen E, Tiitinen H: Serum levels, urinary excretion, and side-effects of cycloserine in the presence of isoniazid and p-aminosalicylic acid. Scand J Respir Dis 1969; 50(4):291-300

In low income countries the incidence of HIV-1 infection in MDR-TB and XDR-TB patients is common. Studies evaluating drug-drug interactions between second-line anti-TB medicines, including PAS, and anti-retrovirals have not been conducted to date. Considering the PK parameters of PAS and its metabolic profile it is proposed that significant interactions are unlikely and thus it is recommended to use standard dosing regimens of PAS to treat in co-infected HIV patients.

2.4.3. Pharmacodynamics

Mechanism of action

According to the literature, para-aminosalicylic acid is bacteriostatic against *Mycobacterium tuberculosis*.

The mechanism of action of para-aminosalicylic acid resembles that of sulfonamides, competing with paraminobenzoic acid (PABA) for dihydropteroate synthetase (dhps), a key enzyme in the biosynthesis of folates. Para-aminosalicylic acid appears to be a weak inhibitor of DHP *in vitro*, raising the possibility that it may have a different and/or additional target within the folate synthesis pathway.

In general the selection of resistant strains by antibacterial agents that inhibit folate synthesis is a relatively common and hence problematical phenomenon.

Primary and Secondary pharmacology

In vitro studies[17] revealed that a concentration of 1.5µg/mL of PAS is sufficient to inhibit the growth of mycobacterium tuberculosis but this is not elaborated upon.

The study by Peloquin in 1994 showed that plasma levels of PAS exceeded the MIC for TB (1-2 µg/mL) for over 24 hours with the recommended posology of 12 g/day given in three divided doses. In the view of the investigators, the MIC level obtained for Paser was above that required for therapeutic activity for over 24 hours as according to several references the MIC for PAS ranges between <1 and 2µg/mL.

According to the applicant, the MIC level and time above this level (1 and 2 µg/mL) was considered to be the predictor of therapeutic activity as up to 20 years ago it was common practice to select the dosage regimen for an antibiotic to achieve blood levels above the MIC for the entire dosing interval. This approach was initially based on clinical experience with agents that were not rapidly bactericidal, e.g. the sulphonamides, tetracyclines and penicillin. Since then the relevance of the PK-PD relationship to the efficacy of some antibacterial agents has been debated and for most antibiotic classes other PK/PD indices have been shown to drive efficacy. These are either: Cmax/MIC, AUC/MIC or time > MIC. It is not fully elucidated which parameter drives response to PAS.

[17]Sievers O: Experimentella försök med para-aminosalicylsyra (PAS) och olika slag av bakterier Sv Lükartidn 1946; 43: 2041

Relationship between plasma concentration and effect

Frequency of dosing

The minimum frequency of dosing for a standard 4g dose of PAS-GR was evaluated within a set of sequential studies (Peloquin 1999). The serum concentrations achieved following 8 days of treatment with either 4 g given twice (BID) or once daily (OD), respectively in two groups of 6 MDR-TB patients each were measured. After twice daily dosing the median (range) steady-state plasma concentrations after a one week-treatment were 25.8 (4.2-53.2) µg/mL at 4h post dose, 23.3 (1.6-51) µg/mL at 8h post dose and 16.4 (5.6-44.5) µg/mL at 12h post dose, respectively. As can be seen, plasma concentrations were relatively stable over the sampling period. Conversely after OD dosing, plasma concentrations were 23.4 (14.6-30.3) µg/mL at 6h post dose but dropped to 3.7 (1.6-13.8) µg/mL at 12h post dose and to nil at 24h post dose. According to the applicant these results indicated that PAS-GR when administered twice daily but not once daily provided levels above the MIC for the entire dosing

In the Peloquin 1999 study, data from 40 MDR-TB patients (14 females, 26 males) on chronic treatment (duration not specified) with 4 g PAS-GR twice daily was evaluated. Median plasma levels were 24.83 (0-95.57) µg/mL within 4-8h post dose and 20.58 (0-90.51) µg/mL within 9-12h post dose. According to the applicant these results confirms that the BID dosing provides MIC above 1 µg/mL over the day in long-term treatment. Only 2/88 plasma concentrations determinations were nil and only 5/88 were lower than 1µg/mL. It confirmed that adequate concentrations were achieved during long-term treatment with a twice daily dosing of 4 g PAS-GR.

Regarding dosing in children, a study with slow release PAS conducted in S Africa (*Liwa* et al., 2012), indicates that PAS at 150 mg/kg daily dosage divided in 1 or 2 gifts would provide similar exposure as in adults.

Dose effect

In chronic use of PAS-GR median levels of PAS were relatively steady over the 4h-periods allowing pooling data of the 3 time points to evaluate the difference in PK after the initial single dose in volunteers and PK at steady-state after a multiple dose regimen in TB patients (Peloquin 1994). Median plasma levels of approximately 10µg/mL after the first dose rose to 28.5 µg/mL after 1 week of a multiple dose regimen (4 g tid), indicating accumulation of PAS with a multiplication by a median factor of 3.5 of plasma concentrations (Peloquin 1994).

Based on findings of the two studies above it is not justified to use doses of PAS higher than 4 g per intake.

Implications of different formulations of PAS on the PK-PD profile

The original studies of the efficacy of PAS (British Medical Research Council 1950, Tuberculosis Chemotherapy Centre 1960) used the sodium salt. Since then several different formulations of PAS were developed with the aims of reducing the gastrointestinal (GI) side effects and extending the half-life to enable fewer administrations per day as, at the time, the target PK-PD parameter was the duration of the serum level of PAS exceeding the MIC.

It was clear from several studies that the different forms of PAS presented different PK profiles. Figure 2, from the Wan 1974b study shows the PK profile of the sodium, potassium and calcium salts of PAS and the free acid.

Figure 2

Figure 5: PK profiles of various forms of PAS (Wan 1974b)

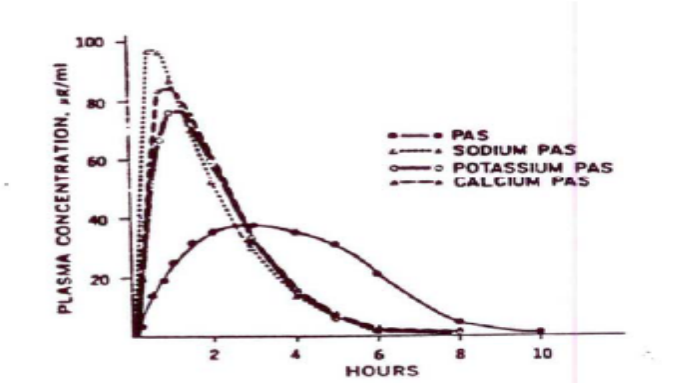


Figure 1—*Mean plasma concentrations of unchanged drug from 12 subjects following administration of four different preparations of aminosalicylic acid (PAS). Data were corrected to 70 kg body weight.*

A resin complex formulation of the free acid, designed to release the drug more slowly in the small intestine so as to reduce gastro-intestinal toxicity and to extend the half-life was approved in the US and Europe (Rezipas DESI 1969). The PK profiles of this product, the salts and the free acid were compared in a study[18]. The free acid (PAS) and the resin complex form of PAS tended to show lower and delayed peak plasma concentrations, just like PAS-GR.

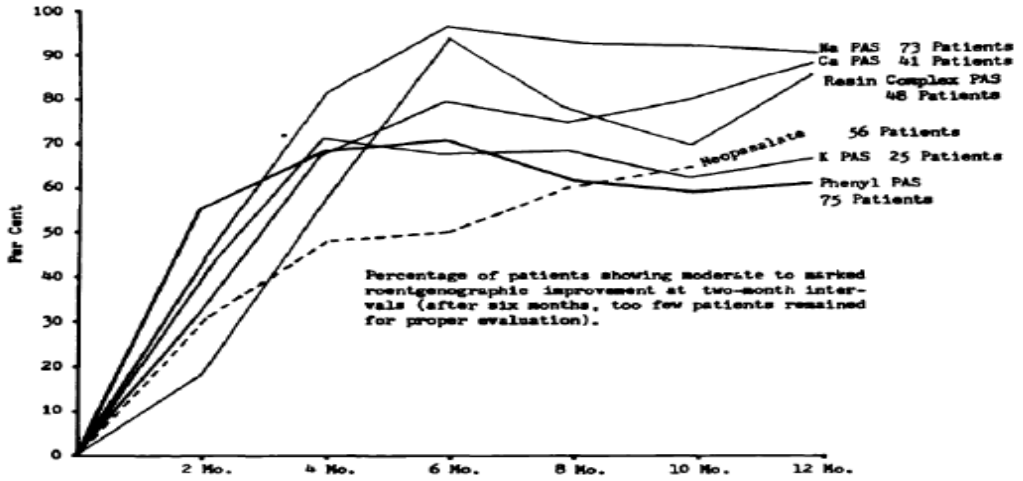
PAS free acid and PAS resin showed a delayed absorption and reduced Cmax when compared to the PAS salts. The delayed absorption has been reported to be due to either the lower solubility of the free acid in aqueous conditions in the small intestine or to the slower release from the resin complex.

These differences in PK profile between the rapidly absorbed salts and PAS in the form of the free acid or that of the resin complex were not considered to affect the efficacy of the drug against *M. tuberculosis* as all agents met the surrogate marker of time above MIC. Moreover, X-Ray data from 318 patients showed no statistically significant differences between 6 formulations in clinical improvement from after 2 months treatment (Figure 3). Bacteriologic analyses also indicated that the 6 formulations were equal in preventing or postponing the development of TB resistant to isoniazid or to other antimicrobial drugs administered in 709 patients (Yue 1966).

[18] Cohen SS, Yue WY, Tsai SH: Comparison of tolerance and absorption of phenyl p-aminosalicylic acid with several p-aminosalicylic acid preparations. Antibiotics Annual 1958; 59:121-124

Figure 3

Figure 6: Improvement in X-Ray assessments in patients treated with various forms of PAS (Yue 1966).



Very little information exists on the relevant PK/PD relationships for second-line agents used to treat MDR-TB. The documented clinical efficacy of PAS combined with relatively infrequent resistance justifies its use as a bacteriostatic second-line drug (Dartois 2010).

According to the applicant, in a review of PK/PD parameters of anti-TB drugs, PAS, as a bacteriostatic agent, has surprisingly higher Cmax/MIC and AUC/MIC ratios when compared with the bactericidal agents such as isoniazid and rifampicin (Budha 2008). As a bacteriostatic agent it may be that the time above the MIC may be the most important parameter; however no ultimate evidence is available.

Peloquin's group in the US recommends administration of PAS-granules to keep inhibitory concentrations above the MIC for most of the dose interval and to target a Cmax of 20-60 µg/mL which occurs at approximately 6 hours post dose with Paser (*vs*. 2 hour post dose with the earlier tablet forms). They recommend a dose increase if the Cmax is below 10µg/mL (Peloquin 2002).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Absorption

In the pivotal PK study (Peloquin 1994), the median time to peak concentration for PAS-GR was 6 hours with a range of 1.5 to 24 hours (delayed in comparison to earlier formulations) and plasma concentrations PAS-GR peaked with a (range) of 15.25µg/ml (9.36- 35.4). These values appear to be lower than what has been described for earlier and other formulations of PAS (PAS Na, PAS K and PAS Ca), which would fit with the anticipated formulation effects. It should however be noted that there is a lack of clarity regarding the assay methodologies of the quoted references. Therefore it is not clear whether any cross-study comparison will be valid.

Food effect

One literature reference is provided to describe the effect of food on PAS-GR, this appeared to show that the AUC of PAS-GR increased with administration of food. However, other drugs were co-administered and the effect of these drugs on the PK of PAS is not known or evident from the references.

Distribution, metabolism and elimination

PAS appears to be relatively bound to albumin, this binding appear to become saturated with increase in plasma concentrations of PAS. The major metabolites of PAS are para-aminosalicyluric acid and N-acetyl para-aminosalicyclic acid as they appear to constitute 90% of the total metabolites. However, it is unclear what the effect of genetic polymorphism on PAS is. PAS and its metabolite Ac-PAS appears to be primarily cleared via the kidneys. From the Peloquin 1994 study, the plasma half- life of PAS-GR was estimated to be approximately 1.62 hours; this said to be higher when compared to earlier formulations.

Special populations

The results of the study that was done in patients with renal and hepatic impairment showed that the PK of PAS was unaltered in patients with hepatic impairment. However, no conclusion can be made as there is a lack of clarity regarding the severity of the hepatic impairment. This same study also showed that in patients with terminal renal failure and on chronic dialysis there was an increase in plasma clearance of PAS. However, no conclusion can be made regarding these results. In the absence of data regarding use in patients with renal impairment, warnings have been included in sections 4.3 and 4.4 of the SmPC.

Children

Data from a study conducted in South Africa (Liwa 2012) substantiate the proposed posology in children. 10 children were included in the study and were given 75mg/kg bid on the first visit and 150mg/kg OD on the second visit. The Cmax after the 75mg bid and 150mg OD regimen were 45.4 µg/ml and 56.5 µg/ml, respectively and the AUC0-12 were 233.3 and 277.9 µg/hr/ml, respectively. These results obtained in visit 1 and 2 were apparently not different statistically from each another and from the results obtained in adults. Additionally, the mean and median plasma concentrations were above the MIC for *M.tuberculosis* during the sampling period (12 hours). However, there was a very high variability and the mean 12 h concentration was 6.8±6.7 µg/mL and 21.2±29.6µg/mL after 75 mg/kg BID or 150 mg/kg OD, respectively; also, a number of children had individual plasma concentrations falling below MIC. Therefore 150mg/kg given daily is probably the barest minimum required to achieve accumulation and a sustained concentration in children.

Interactions

It appears that PAS might interfere with the PK of other antituberculosis drugs. It is suggested that PAS prolongs the T1/2 and also cause decreased albumin binding of isoniazid in rapid acetylators. It also appears that PAS prolongs the half-life of cycloserine. Additionally, it is suggested that PAS interferes with the absorption of Vitamin B12 and digoxin. Overall it is considered that the PK drug-drug interactions for PAS have been incompletely characterised. No studies or literature references have been identified which adequately addressed these specific issues.

It is unlikely that the applicant would be able to carry out the whole range of studies normally required as this application is based entirely on bibliographic references. However, these gaps have been highlighted in the SmPC.

Pharmacodynamics

Overall the pharmacodynamic action of para-aminosalicylic acid appears to be poorly characterised. However, PAS is considered to be bacteriostatic against *Mycobacterium tuberculosis*.

Para-aminosalicylic acid appears to be a weak inhibitor of DHP in vitro, raising the possibility that it may have a different and/or additional target within the folate synthesis pathway.

According to the references provided, the MIC for PAS is most likely between 1 and 10µg/mL.

The PK/PD relationship is also unclear but it has been suggested to be the time above MIC based on historical data.

There is no description of the pharmacodynamic action of PAS when used in combination with other anti-tuberculosis drugs. It is would appear that none of the other anti-tuberculosis agents act via the folate synthesis pathway and it is unlikely that there is a potential for them to compete with or oppose PAS at the receptor level.

In the Peloquin study, when 4g of PAS-GR was administered, the Cmax was reduced and absorption delayed in comparison to the various salts of PAS (Na, Ca and K) and the free acid. According to the applicant, PAS-GR should be administered to keep inhibitory concentrations above the MIC for most of the dose interval and Cmax should be targeted between 20-60µg/ml as Tmax is expected to occur approximately 6 hours post-dose. It appears that with twice daily dosing of PAS-GR steady-state plasma concentration remain relatively constant for up to 12 hours in contrast to the once daily regimen where plasma concentrations dropped by 12 hours post-dose.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

In conclusion, the pharmacokinetics of para-aminosalicylic acid has been broadly characterised and it appears that PAS is primarily metabolised via acetylation to N-acetyl para-aminosalicylic acid and it is excreted mainly through the kidneys. There is a lack of knowledge regarding DDIs, transporter systems and excretion via the renal pathway but these gaps have been highlighted in the SmPC.

The performance of the current PAS product is expected to be the same as that tested by Peloquin et al.

Pharmacodynamics

The suggestion for the PK/PD relationship is the time above MIC but other parameters might be of relevance. Data from a South African study showed similar PK parameters between adults and children.

2.5. Clinical efficacy

2.5.1. Dose response studies

No formal dose response studies were submitted. This application is based entirely on literature references in line with article 10a of Directive 2001/83/EC.

2.5.2. Main studies

According to the applicant, two studies reported in the literature can be considered as pivotal in establishing that PAS is effective in the treatment of TB.

- **Tabular overview of clinical studies (Table 2)**

Reference	Products Dose (g) frequency and duration	Endpoints	Number of subjects	Country	Endpoints Results
British Medical Research Council 1950	- PAS-Na 20 g/day (5 g x 4/day) - Streptomycin 1 g/day by IM - PAS-Na 20 g/day (5 g x 4/day) + Streptomycin 1 g/day by IM	- X-Ray improvement - mortality - weight gain - sedimentation rate - sputum examination and culture - streptomycin sensibility	166 TB-patients of 15-30 years N=59 for PAS-Na N=54 for Streptomycin N=53 for combination	UK 3-month treatment and 3-month follow-up	PAS-Na + streptomycin (SP)> streptomycin (S)> PAS-Na (P) > bed-rest **- X-Ray improvement at 6 months:87% SP vs 74% S vs 56% S** - Mortality at 6 months: 2% SP vs 9% S vs 3% P (NS) - Weight gain at 6 months: NS but gain during the 1st 3 months then reverse values for the next 3 months. - Statistical difference in the fall of sedimentation rate in combination group compared to 2 other groups. **- 33% negative results of sputum culture in SP vs 19% in S group.** - Streptomycin sensibility at 6 months: 89% of the SP patients producing positive cultures had completely sensitive strains and 21 % of the S patients.
Tuberculosis Chemotherapy Centre 1960	- PAS-Na 10 g+ Isoniazid 200 mg bid (1 cachet of 25 mg of isoniazid and 1.25 g of PAS-Na i.e. 0.2-0.3 mg/kg of PAS - Isoniazid 400 mg oad vs 400 mg bid vs 200 mg	- X-Ray improvement - mortality - weight gain - sputum culture - ESR (erythrocyte sedimentation rate)	341 TB-patients from 12 years N=96 with 6 patients receiving PH excreting isoniazid-R strains at inclusion vs 3 isoniazid regimens N=95 vs N=75 vs N=75	India Home treatment Less than 2 weeks of previous Chemotherapy 12-month treatment	PH=PAS-Na + isoniazid group HI-1=400 mg single-daily dose of isoniazid group HI-2=400 mg twice-daily dose of isoniazid group H=200 mg twice-daily dose of isoniazid group - Weight gain at 12 months: 90% in 82 PH, 90 % in HI-1, 69% in HI-2 and 69% in 81 H. - Mortality at 12 months: 3% (90 PH) vs 1% (70 HI-1) vs 3% (68 HI-2) vs 6% (87 H). - X-Ray improvement at 12 months: 85% of PH vs 78% of HI-1 vs 71% of the HI-2 vs 62% of H. - Negative sputum culture at 12-month: 90% of the PH vs 76% of HI-1 vs 59% of HI-2 vs 51% of H. - Bacteriologically quiescent at 12 months: 86% of PH vs 67% of HI-1 vs 56% of HI-2 vs 44% of H.

British Medical Research Council. Treatment of pulmonary tuberculosis with Streptomycin and para-amino-salicylic acid (1950)

The first of these was a controlled trial[19] coordinated by the Medical Research Council in the UK. In this study 166 patients aged 15-30 years presenting with bilateral pulmonary TB categorized on X-Ray classification were randomly allocated to receive one of the following 3 treatment regimens for 3 months with a further 3 month-follow-up period (where the treatment was either collapse therapy or streptomycin in the PAS group). The outcome at 6 months is reported hereafter. Patients were randomized and treated as follows:

1. Streptomycin 1g per day by single IM injection (N= 54)
2. PAS 20 g of the sodium salt per day given in four divided doses, *per os* (N= 59)
3. Streptomycin 1g/d and PAS 20 g/d as above (N=53)

According to the applicant, although this old study was not GCP compliant (*e.g.* patients were unaware that they were participating in an investigation), its methodology is well described and appropriate statistics were relevant to the comparison of streptomycin *vs.* PAS groups. These groups can be justifiably compared as they are well balanced and with an important number of similar subjects. Various endpoints including clinical (temperature, sedimentation rates), radiological, and bacteriological assessments (bacteriological content of the sputum, bacterial drug resistance) were assessed in the study. Statistical methods are not described and no test or p-value is given; it is only mentioned that any observed differences were statistically significant.

Through historical comparison with a former study from the Medical Research Council in 1948 in which the control group were treated with bed rest only, this present study showed that PAS given alone had a clear beneficial effect when compared with no treatment (bed rest alone) in the previous trial.

Results demonstrated that collapse therapy was similar in both groups in the follow-up period (it occurred in 20 PAS patients compared with 22 streptomycin patients) as well as at each time point. Clinically, responses were equally rapid in streptomycin and PAS groups and weight gain similar after six months. There were 2 (3%) patients deaths and 4 cases (7%) deteriorated (radiological assessment) during treatment with PAS, which historically can be compared to 14 (27%) deaths and 18 (34%) deteriorations in untreated patients, and is compared to 5 (9%) deteriorations and 5 (9%) deaths with streptomycin alone in the same trial. On X–Ray evaluation, PAS was found to be statistically (test not described) less effective than streptomycin alone (improved patients: 33 (56%) *vs.* 40 (74%), respectively).

In the sixth month the number of patients with negative bacteriological results (via direct examination and culture) were significantly higher (test not described) in the combination group than in the two other monotherapy groups with 28 (33%) vs. 16 (19%) and 6 (8%) for streptomycin and PAS, respectively. When given in combination there was a dramatic decline in the development of streptomycin-resistant bacterial organisms: 33 out of 49 (67.3%) patients developed resistant organisms in the streptomycin treated group compared with 5 out of 48 (10.4%) patients receiving the combination. At the end of the six month-period 89% of the combination patients producing positive culture had completely sensitive strains vs. only 21% of the streptomycin alone patients.

[19]British Medical Research Council: Treatment of pulmonary tuberculosis with Streptomycin and para-amino-salicylic acid. BMJ 1950; Nov (11):1073-1085

According to the applicant, this study also supported the notion that streptomycin resistance was responsible at least in part for failure of the drug to prevent clinical deterioration and that the better results obtained with combination to PAS were due to maintenance of streptomycin sensitivity. The study showed that this effect was maintained up until the sixth month of follow-up despite the treatment had only lasted 3 months.

Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in south India (1960)

The second study[20] evaluated the efficacy of PAS given in combination with isoniazid compared to the efficacy of three different regimens of isoniazid alone in Madras, India.

In this prospective, double-blind, controlled trial 341 patients aged over 12 years (only 2 patients were less than 15 years, both belonging to the combination group) were included. They presented with acute pulmonary TB with a positive bacteriological testing on a minimum of 4 sputum specimens and were randomised to receive 12 month-combination therapy with:

- PAS plus isoniazid standard dose (N= 90) or
- One of three different schedules of isoniazid monotherapy (N=87 for isoniazid standard dose group).

The follow-up lasted five years. The dosages of PAS and isoniazid used were based on patients' weight. The mean daily dose at the start of treatment was 0.23 g/kg (the standard dose was 10 g/d and ranged from 7.5 to 10 g/d according to body weight) for PAS (given twice daily as the sodium salt of PAS) and 4.6 mg/kg for isoniazid in the combination therapy group, and 8.7 mg/kg (i.e. a double dose, given in a single or in 2 separated doses) and 4.5 mg/kg (given twice daily) in the monotherapy groups (the standard dose was 200 mg/day and varied depending on body weight).

The study was methodologically acceptable (double blind) though not GCP compliant as there was absence of informed consent and recording of religious information). Moreover, there were some statistically significant ($p<0.01$) pre-treatment differences between groups in the extent of cavitation for the combination group as 15 (17%) patients had gross extent cavitation compared with 8 (9%) in the standard dose isoniazid monotherapy group.

The radiographic spread of tuberculosis occurred in 26% and 21% in each group, respectively, and hence despite pre-treatment differences, (cf. above) after over 12 full months, 85% of the combination and 62% of the comparable dose isoniazid monotherapy group showed a moderate or greater improvement. Over the year of treatment 35 patients had their treatment changed because of clinical deterioration with a strikingly significant difference of only 1 patient vs. 15 ($p<0.001$) in the combination and isoniazid standard treatment groups, respectively.

At 12 months, negative cultures were seen in 90% of patients treated with PAS and isoniazid compared with 51% of patients with the comparable dose of isoniazid monotherapy regimen, a difference statistically significant ($p<0.01$). Resistance to isoniazid emerged within 1 month in the monotherapy groups and more slowly in the combination therapy group. At 12 months, 8% of patients in the PAS plus isoniazid group had isoniazid-resistant bacterial organisms vs. 47% of patients who received the comparable dose of isoniazid monotherapy. At 12 months 86% vs. 44% ($p<0.01$) were bacteriologically quiescent among the two groups above, respectively. The authors

[20] Tuberculosis Chemotherapy Centre, Madras: A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. Bull Wld Hlth Org 1960; 23:535-585

concluded that the potential public health risk from excretors of isoniazid-resistant organisms was appreciable with isoniazid monotherapy; a risk that started early in therapy and continued throughout the 12-month therapy period.

When comparing the combination group to the equivalent dose of isoniazid monotherapy group, only one patient of the 3 who died vs. 4 of the 4 who died, actually died from pulmonary tuberculosis.

According to the applicant, these two pivotal trials converge in demonstrating the statistically significant benefit of combination therapy with 12-20 g/d PAS for 3-12 months over monotherapy of either isoniazid or streptomycin on clinical, radiological and bacteriological endpoints in a representative number of patients with pulmonary TB.

Supportive studies

Several controlled clinical trials carried out at the Tuberculosis Chemotherapy Centre in Madras, India or in the UK by the British Medical Research Council are considered by the applicant to be supportive of combination therapy with PAS in treating active TB (Table 3). For a series of methodological reasons summarized in the table, these studies can only be considered as supportive to the efficacy of PAS. However, the high numbers of patients exposed for long periods of time to treatment with PAS are of particular interest for the safety evaluation.

Table 3: Summary of efficacy results in supportive clinical trials conducted with PAS Na

Author Reference	Number of patients evaluable	Objective	Methods	Results
Selkon Tuberculosis Chemotherapy centre Madras Bull Wld Hlth Org. 1964; 31: 273-294 **India**	*cf. pivotal trial n°2 above*	To evaluate the emergence of isoniazid resistant organisms and evaluate the degree of resistance in resistant bacterial organisms	Sub-analysis of the 2nd pivotal trial (*cf.* above). Discussion only on 2 groups: combination *vs.* same dose of isoniazid monotherapy Degree of resistance and month of emergence of isoniazid resistant strains in slow and rapid isoniazid inactivators	Resistant strains: Combination group 16 (8 in slow inactivators, 8 in rapid inactivators) *vs* 57 (30 slow, 25 rapid, 2 ND) in isoniazid monotherapy group Month of emergence of resistance (Combination *vs.* isoniazid H): 1-2: 1 *vs.* 32 3-4: 3 *vs.*11 5-6: 8 *vs.* 10 7-12: 4 *vs.* 4
Tuberculosis Chemotherapy centre Madras Bull Wld Hlth Org. 1964; 31: 247-271 **India**	150 isoniazid +streptomycin: 79 isoniazid +PAS-Na: 71	To evaluate continuous *vs.* intermittent dosage regimen	Fully supervised regimen *vs.* unsupervised regimen Twice weekly administration *vs.* daily dosage isoniazid 650 mg + STP (1g IM) *vs.* isoniazid 200 mg + PAS-Na (0.2-0.3 g/kg/d or 10 g daily)	Multiple combined comparisons therefore not suitable for efficacy analyses

Author Reference	Number of patients evaluable	Objective	Methods	Results
			Exposure: 12 months	
Dawson Tuberculosis Chemotherapy centre Madras Bull Wld Hlth Org. 1966; 34: 483-515 ***Publication not provided*** **India**	220 isoniazid +PAS: 72 isoniazid +Thioacetazone: 77 isoniazid +PAS 2 steps: 71	To evaluate various combination therapy in ambulatory treatment	isoniazid (4.5 mg/kg/d) + PAS (0.22 g/kg/d) *vs* isoniazid (6.9 mg/kg/d) + thioacetazone (3.4 mg/kg/d) in o.a.d dosing *vs* a two step-regimen with isoniazid (5.5 mg/kg/d) + PAS (0.17 g/kg/d) for 6 month followed by isoniazid (6.8 mg/kg/d) Exposure: 12 months	Multiple combined comparisons and variable dose regimen of each drug in each group therefore not suitable for efficacy analyses
Dawson Bull Wld Hlth Org. 1966; 34: 533-551 **India**	193 96 ambulatory 97 hospitalized (sanatorium)	Five-year follow-up in hospitalized *vs*. ambulatory patients	Dose regimen: isoniazid 0.2-0.3 g/kg) + PAS-Na (4-6 mg/kg/d) for 12 months then isoniazid (4-6 mg/kg/d) *vs*. placebo	The efficacy at 12 months ranges between 73% and 86%
Ramakrishnan 1969 **Quiescent pulmonary TB patients** **India**	119 isoniazid +streptomycin: 66 isoniazid +PAS: 53	Four-year-follow-up in 2 different combination groups	Dose regimen: isoniazid high dose (12.5-16.1 mg/kg/d) + streptomycin (1g) IM twice/wk *vs*. isoniazid (4.4 mg/kg/d)+PAS Na (0.22 g/kg/d) for 12 months. Then isoniazid (400 mg for 12 months or 300 mg for 6 months) *vs*. placebo	isoniazid+streptomycin: 8 bacteriological relapses 3 re-treatment isoniazid +PAS: 8 bacteriological relapses 5 retreatment 1 death from TB
Tuberculosis Chemotherapy centre Madras Tubercle 1973; 54: 23-43 **New pulmonary TB patients (with positive sputum), Randomization** **India**	415 (359 analysed) isoniazid + streptomycin: 181 *vs.* isoniazid + streptomycin +PAS: 178	To compare 2 combination therapy: isoniazid + streptomycin 1g or isoniazid + streptomycin 0.75 g *vs.* isoniazid + streptomycin 1g +PAS or isoniazid + streptomycin 0.75 g + PAS	Dose regimen: isoniazid 400 mg/d for 1 month followed-up by 13-17 mg/kg once a wk + streptomycin 1 g/d (or 0.75 g/d) *vs.* same combination+ PAS-Na 6 g/d Duration of exposure: 12 months	Treatments were equivalent with 85% *vs.* 87% favourable bacteriological response isoniazid + streptomycin group: 2 deaths from TB and 4 radiological/clinical worsening (none in the other group) Resistance to isoniazid: 8% *vs*. 5% in isoniazid + streptomycin and isoniazid + streptomycin +PAS groups,

Author Reference	Number of patients evaluable	Objective	Methods	Results
				respectively 60/178 pts with plasma concentrations of PAS: in fast isoniazid acetylers PAS concentrations were too rapidly excreted to delay the acetylation of isoniazid
British Medical Research Council Tubercle 1973; 54: 99-129 **New pulmonary TB patients (with positive sputum), randomization, controlled** **UK**	481 (412 analysed) isoniazid + streptomycin + PAS-Na: 109 or isoniazid + streptomycin + EMB: 97 or isoniazid + streptomycin +rifampicin: 103 or isoniazid + streptomycin + PAS-Na followed up by isoniazid high dose + streptomycin: 103	Effectiveness of 4 different chemo regimens	isoniazid + streptomycin + PAS-Na 12 g/d or isoniazid + streptomycin + EMB or isoniazid + streptomycin +RMP or isoniazid + streptomycin +PAS-Na followed up by isoniazid high dose + streptomycin Duration of exposure to triple therapy: 3 months with 9 additional months	The speed of elimination of acid-fast bacilli in the smear was similar in the 4 groups and significantly faster in the RMP combined group than in the others. 96% patients treated with PAS had favourable bacteriological response at 12 months
Tuberculosis Chemotherapy centre Madras BMJ 1973; 2: 7-11 **New pulmonary TB patients (with positive sputum)** **India**	247 (173 analysed) isoniazid + PAS-Na biweekly: 122 (90 analyzed) isoniazid + PAS-Na daily: 125 (83 analyzed)	To evaluate fully supervised twice weekly *vs.* self-administered daily treatment	streptomycin (1g/d)+ isoniazid (400 mg/d) + PAS-Na (6 g/d) for 2 wks then randomization to either isoniazid (15 mg/kg)+ PAS-Na (0.2 g/kg) twice per week or isoniazid (4.7 mg/kg/d)+ PAS-Na (0.2 g/kg/d) Duration of exposure: 12 months	Equivalent efficacy at 12 months 88% *vs.* 87% having a favourable bacteriological response

PAS: para-aminosalicylic acid, EMB: Ethambutol, RMP: Rifampicin

These supportive trials have been carried out in a total of 1626 (mainly adult) patients with pulmonary tuberculosis, among who 920 received PAS in a combination therapy group. The duration of treatment with PAS-combination was 12 months and in the majority of cases the dose was between 0.17 and 0.3 g/kg/day (*i.e.* 10-15 g/d) except in 2 studies which evaluated a lower dose of 6 g/day PAS (Tuberculosis Chemotherapy Center 1973; BMJ 1973). Bacteriological efficacy results were favourable to the combination with PAS, provided the dose was sufficient. This was clearly shown on the incidence and speed of emergence of resistant strains as compared to isoniazid monotherapy (Selkon 1964).

Most of the studies detailed above are further elaborated in the safety section and not always the same numbers of patients are reported for the efficacy and safety section.

More recent studies specifically in MDR-TB have been performed in India (*e.g.* Prasad 2006). Multiple second line treatments (including 0.15 g/kg/day PAS in two separate intakes) were associated with

therapeutic efficacy of 74% bacterial conversion in 46 hospitalized patients (13-62 year-old; 24-64 kg) who were resistant to at least five first line drugs. Despite the fact that it remains difficult to attribute the individual benefit to one drug or the other, it points towards a very favourable effect of PAS.

2.5.3. Discussion on clinical efficacy

Para-aminosalicylic acid gastro-resistant granules (PAS-GR) has been proposed for the treatment of tuberculosis in combination with other active agents, especially in multi-resistant TB or in situations when primary medication therapy with recommended agents is not possible due to a combination of resistance and or intolerance.

This is a bibliographic application and no clinical studies have been conducted and demonstration of efficacy of this product relies entirely on historical literature references.

Design and conduct of clinical studies

The two pivotal references and the supportive references were all conducted pre-GCP and therefore not entirely in line with GCP principles.

Efficacy data and additional analyses

The study by the Medical research council showed that 56% of the patients that were given just PAS improved on x-ray assessment compared with 87% in the group that were given a combination of streptomycin and PAS. However, when compared with bed rest alone, PAS appeared to be better. In terms of bacteriological assessment of sputum, PAS in combination with Streptomycin appeared to be better than PAS alone or streptomycin alone (in the 6th month of treatment, 33% of the combination group had negative cultures compared with 8% in the PAS group). Additionally, when PAS was given in combination with streptomycin, the emergence of streptomycin resistance was reduced as 89% of the combination group had sensitive strains compared with 21% of the streptomycin only group.

In the study by the Tuberculosis Chemotherapy Centre there was a rapid decline in the proportion of patients with positive cultures. By 3 months, 78% of the patients who were given PAS + isoniazid had negative cultures. On x-ray assessment 63% of the patients on PAS and isoniazid who had moderate cavitations at the start of treatment had no cavitations at 12 months. Also, it appears that when PAS was given in combination with isoniazid the incidence of isoniazid resistant organisms was reduced in comparison to the isoniazid only groups.

In terms of the use of PAS in the treatment of MDR-TB/XDR-TB, these two studies provide some evidence that PAS or PAS-GR could be useful in the treatment of multi-drug resistant tuberculosis (MDR-TB) and extensively-drug resistant tuberculosis (XDR-TB) as the emergence of resistance was lower when PAS was co-administered with either streptomycin or isoniazid.

The results from the other literature references support the effectiveness of PAS in the treatment of active TB when used in combination with other drugs. A recent study in 46 previously treated tuberculosis patients, presenting with MDR-TB and given a regimen containing PAS at 150 mg/kg/day in two divided dosages, showed sputum culture conversion in 29 out of 39 hospitalised patients (74%) after mean time of 4.4 months.

Additional expert consultation

No additional experts were consulted during the assessment.

Assessment of paediatric data on clinical efficacy

The applicant provided data from a study conducted in South Africa (Liwa 2012) to substantiate the proposed posology in children (see *Pharmacokinetics* section for details).

The proposal is for the dosage to be adapted to the patient's weight at 150 mg/kg/day, divided in two to three intakes. However, for a 50 mg/kg thrice daily dosage recommendation, no PK/ PD data have been provided in support. In fact, a higher dosage of 75 mg/kg t.d.s could have some advantages but currently no information is available around its potential adequacy. As such, the CHMP recommends that the proposed dosage, adapted to the patient's weight at 150 mg/kg, be divided in two intakes daily.

In view of the submitted data, the CHMP considers that PAS has a recognised efficacy in terms of the conditions set out in Annex I of Directive 2001/83/EC.

2.5.4. Conclusions on the clinical efficacy

In conclusion, the references provided by the applicant suggest that when PAS was used in combination with other anti-tuberculosis drugs (Streptomycin and Isoniazid), it could be effective in the treatment of active TB. It also appears to reduce the incidence of resistant organisms. It is therefore considered that PAS can make a contribution as part of a treatment regimen for MDR-TB or XDR-TB. It is possible to assume that if the MIC for *Mycobacterium tuberculosis* remains within the normal population distribution then there is a potential that PAS may assist in the overall treatment regimen.

In view of the submitted data, the CHMP considers that PAS has a recognised efficacy in terms of the conditions set out in Annex I of Directive 2001/83/EC.

2.6. Clinical safety

When PAS was introduced (1946) the incidence of TB was very high in Western Europe and the USA with reported rates in many countries of over 150:100,000. In the UK, where the number of cases has been recorded since 1900, over 80,000 notified cases were reported in 1945 (an incidence of 180:100,000 -NHS Tuberculosis 2006). In France, TB became a disease of mandatorily notification in 1966, and in 1972 its incidence was reported as 60:100,000 with over 30,000 cases (La tuberculose - fr, 2000).

Following the confirmation of the efficacy of PAS and the discovery that combined therapy with isoniazid and streptomycin reduced the development of drug resistance, its use in combination became accepted practice. After extensive use in the treatment of TB, the adverse event profile of the active substance (PAS) is quite well characterized. Different preparations of PAS were developed with the aim of reducing the GI toxicity. Moreover free PAS acid is poorly soluble in water (0.2%) and aqueous solutions of the acid are very unstable and are decarboxylated to meta-aminophenol.

Patient exposure

None directly provided.

The applicant states that the manufacturer of Paser (PAS-GR), Jacobus Pharmaceutical Company Inc, has supplied a total of 781,359 packs to the US and overseas between 1996 and 2010. Assuming each patient is treated for 2 years as per the WHO recommendations and a patient will consume 3 packs per month (one pack is 10 days treatment at one sachet 3 times a day) or 36 packs per year. There are therefore over 21,000 patient-years or if all receive 2 year treatment, over 10,000 patients during this time. Additionally, Paser has been available in South Africa on a named-patient basis since 2008 and a total of 42,649 packs have been supplied from 2008-2010, *i.e.* 580 patients treated for 2 years. It is not possible to determine how many patients in the EEA have received Paser over this period as Jacobus supplies Paser to the WHO and not to individual countries who obtain the product via the Green Light Committee Program. In the EEA Latvia, Lithuania and Estonia have been approved into the Green Light Committee program since 2000 and may have procured Paser for the treatment of MDR- and XDR-TB from the Global Drug Facility. The NGO, Médecins Sans Frontières, also supply Paser and other forms of PAS to developing countries with a high burden of TB throughout the world. Currently they are treating over 2,000 patients with PAS (Ms. Karen Day, *Personal communication* November 2011).

All of the above indicate that PAS has been included in standard treatment regimens for MDR- and XDR- TB in Europe for at least 10 years and hence the use of the product in this indication can be said to be well established and safe as there was no report of SAE published.

Adverse events

In the early and pivotal clinical trial comparing PAS with streptomycin, 34 (58%) patients reported GI side effects including nausea in 22 (38%), diarrhoea in 19 (33%), and vomiting in 14 (24%) with sodium PAS at a dose of 20 g/day alone and in 27 (51%) of patients in the combination group (British Medical Research Council 1950). In a single instance it was necessary to reduce the daily dose of PAS, but no patient had to discontinue treatment. Three patients developed a rash under PAS alone: in two it remained not severe and the treatment could be continued; the other patient developed an extensive rash with fever after 4 weeks of treatment. Four patients developed rashes in the combination group.

In the other pivotal trial (Tuberculosis Chemotherapy Centre 1960), a total of 7 patients had to change treatment because of toxicity; only one case occurred in the combination group (vs. none in the isoniazid standard dose monotherapy group: i.e. all other 6 cases were in the double dose isoniazid monotherapy groups). This change in treatment was due to a hypersensitivity reaction attributed to PAS. Moreover, 3 cases of hypersensitivity to PAS (2 rashes and 1 fever with intense itching) were encountered among the 90 patients in the combination group. An episode of jaundice unrelated-to-treatment but to an intercurrent hepatitis developed in one patient. An episode of isoniazide-related neuritis occurred in one patient from the combination group vs. none from similar dose isoniazide monotherapy group (and 19 in double dose isoniazide groups). Eventually no patient had to receive a reduced dosage of PAS because of an adverse event.

In the study conducted in children (Soderhjelm 1949), no signs of toxicity (leucopenia or vomiting) were reported.

As the original product, PAS free acid, caused acute gastro-intestinal (GI) discomfort very rapidly after ingestion, many patients could not tolerate the medicinal product which could lead to poor compliance in chronic treatment. As the solubility of PAS increases with increasing pH, TB patients

receiving chronic treatment with high doses of PAS, received the sodium salt or co-administration with bicarbonate rather than the poorly soluble free acid in order to minimize the dangers of possible renal damage in (Way 1948). Different preparations of PAS were developed with the aim of reducing the GI toxicity (Yue 1966). Others which were reported to offer better GI tolerance were:

- buffered tablets (Deeb 1955),
- sustained-release tablets of the acid (Small 1958),
- ascorbic conjugate of PAS (Pentikainen 1973),
- PAS adsorbed on to an anionic exchange resin (Hollander 1955)
- phenyl PAS (Cohen 1958)

Sodium salt of PAS was reported to cause less nausea than the free acid formulation (Way 1948). The adverse events profiles of phenyl *p*-aminosalicylate, para-aminosalicylate anionic exchange resin complex, sodium PAS and calcium PAS were actually compared in a first study (Table 4, Cohen 1958).

Table 4: Incidence and severity of GI symptoms in patients treated with various PAS preparations (Cohen 1958)

Symptoms severity n (%)	PAS Na (N=71)	PAS K (N=49)	PAS Ca (N=81)	Phenyl PAS (N=25)	PAS resin (N=117)
none	27 (38)	8 (16)	28 (35)	22 (88)	67 (57)
mild	26 (37)	15 (31)	32 (40)	2 (8)	40 (34)
moderate	15 (21)	24 (49)	16 (20)	1 (4)	9 (8)
severe	3 (4)	2 (4)	5 (6)	0	1 (1)

Furthermore in a total of 192 TB patients treated with various formulations of PAS, the number and severity of moderate and severe symptoms were analysed (Table 5; Yue 1966).

Table 5: Incidence and severity of GI symptoms in patients treated with various PAS preparations (Yue 1966)

Symptoms severity n (%)	PAS Na (N=168)	PAS K (N=53)	PAS Ca (N=101)	Phenyl PAS (N=119)	PAS resin (N=146)	Neopasalate (N=112)	Total
moderate	27 (16)	25 (47)	18 (18)	19 (16)	17 (12)	9 (7.4)	115 (84)
severe	8 (5)	2 (4)	7 (7)	4 (3.4)	1 (0.7)	0	22 (16)
Total	35 (21)	27 (51)	25 (25)	23 (19)	18 (12)	9 (7.4)	137

The reduction in the number of patients reporting GI symptoms with the resin and phenyl forms of PAS in the 2 studies above indicated that it was possible to formulate PAS to improve GI safety when compared with the salts.

GI tolerability of PAS-GR

The development objective for PAS-GR was to provide a therapeutically active formulation of PAS which would avoid the high level of GI side effects seen with earlier forms of the salts and to more resemble the PK profile of later developments such as the resin complex of PAS.

The purpose of PK studies with the PAS-GR formulation was also to evaluate the safety profile and tolerability of single and repeated doses of the product in patients and healthy volunteers (Peloquin 1994, Peloquin 1999, Peloquin 2001). In healthy volunteers receiving a single 4 g dose of PAS-GR, GI symptoms were recorded on visual analog scales (VAS) before and at several time points after dosing. GI side effects were also recorded in the 6 patients receiving PAS granules as part of their MDR-TB treatment regimen (Peloquin 1994). In healthy subjects, seven positive responses for AE potentially due to PAS-GR at any time point were recorded (3.65% of all VAS). There were two reports of mild stomach pain 4 and 12 hours after the dose, respectively; two of mild nausea 1 hour after the dose and three of mild to moderate bloating 1 and 12 hours after the dose, respectively, all in 4 of the 12 subjects. In TB patients, 2 of 6 (33%) developed diarrhoea after approximately 3 days into treatment which resolved over 3 days. A third of patients reported having soft stools during the same time. The drug was continued in all patients (Peloquin 1994).

Using visual analog scales, GI adverse effects were reported by 12 patients in another study with PAS-GR (Peloquin 1999). Several patients reported mild-severe GI symptoms (Table 6).

Table 6: Incidence and severity of GI symptoms in patients treated with PAS-GR (Peloquin 1999)

Symptom: Number (Severity)	PAS-GR 8 g/d (2x4 g)	PAS-GR 4 g/d (OD)
Diarrhoea	4 (2 mild; 1 moderate; 1 severe)	-
Bloating	3 (1 mild; 2 moderate)	3 (3 moderate)
Nausea	-	1 (1 mild)
Total	7	4

PAS-GR was associated with few (11) generally mild or moderate GI adverse effects and no serious adverse events were noted. The granule form of PAS was well tolerated with both dosing regimens (4 g BID or OD).

In the Peloquin 2001 study, in 16 healthy subjects who received 6 g PAS-GR, the reported AEs included: nausea and vomiting, difficulty concentrating, dizziness, headache, diarrhoea, abdominal cramps and metallic taste. The details of each respective AE frequencies are however not provided. It is only mentioned that, in comparison with the regimen under fasting conditions, food modestly decreased the incidences of nausea ($p=0.06$) and that of vomiting ($p=0.1$).

Conclusions on safety

The active principle of PAS-GR (PAS) has been extensively used from the middle of the last century to date and its safety profile is quite well characterized from clinical studies (Table 7). Most frequent AEs were related to the gastrointestinal system (26.4%) and are extensively described above as attempts to reduce these AEs led to the development of several alternative formulations of PAS. Cutaneous hypersensitivity reactions were also frequent (6.3%) as well as AE related to the nervous system (6.1%). Hepatic abnormalities were reported with a relatively high incidence (2.1%). A variety of other AE have also been reported.

Table 7: Incidence of Adverse Events in clinical studies (1079 patients treated with PAS)

Adverse Events	Number of patients with AE in a PAS group	Incidence (%)
GI symptoms not specified	185	17,1
Nausea or vomiting	100	9,3
Cutaneous hypersensitivity	68	6,3
Giddiness/vestibular syndrome	61	5,7
Jaundice	17	1,6
Anorexia	8	0,7
Elevated liver transaminases	8	0,7
Visual abnormalities	3	0,3
Peripheral neuropathy	1	0,1
Fever	1	0,1
Urticaria	1	0,1
Agranulocytosis	1	0,1
Anaemia	1	0,1

Hypersensitivity to PAS is described after a period of exposure to the drug and a delay of about four weeks, in a normally progressively occurring febrile context in a patient previously afebrile (Simpson 1960). A rash or itching of the skin are frequent accompanying symptoms. When the drug was not discontinued hepatic features might have appeared (jaundice, hepatomegaly, and elevated liver enzymes). Hepatic complications of PAS were also quite frequently reported in observational studies (Rossouw 1975). Though not reported in studies in Table 7, moderate hypothyroidism was a well-known complication with PAS related to a direct effect on the synthesis of thyroid hormone (with no interaction with iodine uptake) as shown in 5 euthyroïd tuberculous patients treated for up to 22 weeks with 12-15 g/d sodium PAS (Edwards 1954).

Only a limited proportion of PAS-related AE (7(14%): 5 (10%) GI disturbances, 1 (2%) rash, 1 (2%) fever) actually resulted in treatment discontinuation as shown in one retrospective monocentric study on 171 MDR-TB pulmonary patients (Goble 1993).

The specific tolerability of PAS-GR was studied in healthy volunteers (Peloquin 1994, Peloquin 2001) and in TB patients under the compassionate use program in France (ATU 1st quarterly report) or in clinical studies (Peloquin 1994, Peloquin 1999). The incidence of AE with PAS-GR (Table 8) is therefore based on a much more limited database of 110 subjects than that obtained with all other formulations of PAS. A total of 37 (33.7%) subjects with AE have been recorded. Digestive AE remain the most frequent (23.7%) though with a lower incidence than with previous formulations. A variety of other AE have also been reported; their respective incidence is not always available.

Table 8: Incidence of Adverse Events in clinical studies (110 patients treated with PAS-GR)

Adverse Events	Number of patients with AE in a PAS-GR group	Incidence (%)
Bloating	9	8,2
Diarrhoea/soft stool	8	7,3
Nausea or vomiting	6	5,5
Hypothyroidism	3	2,7
Stomach pain	2	1,8

Neutropenia	2	1,8
Reduced PTT from hypovitaminosis K	2	1,8
Elevated liver transaminases	1	0,9
Hepatocytolysis	1	0,9
Neuropathy	1	0,9
Tendon pain	1	0,9
GI symptoms not specified	1	0,9
Difficulty concentrating	Not specified	
Abdominal cramps	Not specified	
Metallic taste	Not specified	
Headache	Not specified	
Dizziness	Not specified	

In addition despite the limited sample size, under named-patient use ("nominative ATU") in France, a total of 11 children have received PAS-GR since mid-2011 and until today there have been no reported AEs.

These data support the proposition that the enteric-coated, granule form of PAS (PAS-GR), is safe and well tolerated compared with the original forms of the free para-aminosalicylic acid or its salts.

This concurs with the WHO recommendation of the use of the enteric-coated granule forms of PAS, as a Group 4 bacteriostatic agent, as they are well tolerated (WHO 2008; 2011).

2.6.1. Discussion on clinical safety

The only clinical studies that have been conducted with PAS-GR are pharmacokinetic studies provided as literature references (Peloquin studies). Demonstration of safety relies solely on literature references. PAS was used in the latter part of the last century for the treatment of active tuberculosis in combination with other anti-TB medicinal products. It would appear that the use of PAS diminished and was discontinued in many European countries due to its significant adverse gastro-intestinal side effects of nausea, vomiting and diarrhoea. In line with this, most of the side-effects noted in the literature references were mainly gastro-intestinal in origin, although cases of hypersensitivity, giddiness/vestibular symptoms, and jaundice were also noted.

According to the applicant, PAS-GR has been developed to reduce the gastro-intestinal side effects. In the Peloquin PK studies, mild to moderate gastro-intestinal side effects were also noted but the frequencies of these are unknown.

In terms of exposure it is unclear how many people were exposed to PAS when it was commonly used. According to the applicant a total of 781,359 packs of PAS-GR have been supplied to the US and other parts of the world between 1996 and 2010, which means approximately 10,000 patients, may have been exposed to it. It is not clear how many patients have been exposed to PAS-GR or any other forms of PAS in the EU but the applicant considers that Latvia and Estonia have been part of the WHO Green Light Programme since 2000 and therefore may have procured PAS-GR.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Additional expert consultations

None

2.6.2. Conclusions on the clinical safety

Para-aminosalicylic acid is known to have severe gastro-intestinal side effects which lead to discontinuation of its use in many parts of Europe and PAS-GR appears to also present with gastro-intestinal side effects but it is unclear how frequent this is. It also potentially interacts with other anti-tuberculosis drugs but the type and frequency of adverse events as a result of this is not clear.

Overall, it appears the main problem with PAS is its gastro-intestinal side effects. It is unclear however how many patients have been exposed to it in the past 10 years and it is also unclear if PAS is used on a routine basis as second line treatment of MDR-TB or XDR-TB.

In view of the submitted data, the CHMP considers that PAS has an acceptable level of safety in terms of the conditions set out in Annex I of Directive 2001/83/EC.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan *version 1 of 14 November 2013*, the PRAC considers by consensus that the risk management system for para-aminosalicylic acid granules (PAS-GR) in the treatment of multi-drug resistant tuberculosis in combination with other medicinal anti-TB agents is acceptable.

Advice on conditions of the marketing authorisation

The PRAC advises that the following should be conditions of the Marketing Authorisation:

Risk management Plan (RMP)

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:

1. At the request of the European Medicines Agency;
2. 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 submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

The PRAC considers that no additional risk minimisation measures will be necessary for the safe and effective use of the medicinal product.

Obligation to conduct post-authorisation measures

Not applicable

This advice is based on the following content of the Risk Management Plan:

- ***Safety concerns***

The applicant identified the following safety concerns in the RMP:

Table 9: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Hypothyroidism Hypersensitivity reactions Increased toxicity in HIV infected patients Agranulocytosis Drug resistance
Important potential risks	None
Important missing information	Use in children Use in pregnant women Interactions with some other anti-tuberculosis drugs Use in patients with renal impairment

The PRAC agreed.

- ***Pharmacovigilance Plan***

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. This will include targeted follow-up questionnaire for reports of lack of effect and enhanced follow up of all women of child-bearing age to confirm pregnancy and pregnancy outcome. Isolates from cases of treatment failure, which may indicate potential resistance, will be investigated for PAS resistance and the mechanisms of resistance.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures for PAS-GR

Table 10: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypothyroidism	Listed in section 4.8 of SPC Prescription only medicine	None
Hypersensitivity reactions	Desensitisation information provided in section 4.2. Contraindicated in SPC section 4.3 if previous reactions known. Warning in section 4.4 to use with caution for the first 3 months of treatment and discontinue of any signs of reaction. Listed in section 4.8 Prescription only medicine	None
Increased toxicity in HIV infected patients	Information on interactions with anti-retrovirals in SPC section 4.5 Listed in section 4.8 Prescription only medicine	None
Agranulocytosis	Listed in section 4.8 of SPC Prescription only medicine	None
Drug Resistance	Review case reports Prescription only medicine	None
Use in Children	Specific does information in SPC section 4.2. Information on adverse reactions in children in section	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.8. Prescription only medicine	
Use in pregnant women	Information on use in pregnancy in SPC section 4.6 Prescription only medicine	None
Interactions with some other anti-tuberculosis drugs	Information on interactions in SPC section 4.5 Prescription only medicine	None
Use in patients with Renal Impairment	Contraindicated in SPC section 4.3 in patients with severe or end stage renal disease. Warning in section 4.4 to use with caution in patients with mild to moderate renal impairment. Listed in section 4.8 Prescription only medicine	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

PAS was originally (1946) employed as a first-line anti-TB medicine. It was introduced into anti-TB chemotherapy during an era when the benefits of combination drug therapy had been acknowledged but the number of medicines available was quite limited.

It appears that PAS when used in combination with other anti-tuberculosis agents (streptomycin and isoniazid), was effective for the treatment of active tuberculosis.

Beneficial effects

PAS when given in combination with streptomycin or isoniazid reduced the emergence of resistant organisms to both streptomycin and isoniazid. Potentially therefore PAS can make a contribution as part of a treatment regimen for MDR-TB or XDR-TB. It can be assumed that if the MIC for *mycobacterium tuberculosis* remains within the normal population distribution then PAS would contribute to the overall treatment regimen.

The World health organisation (WHO), recommends the inclusion of PAS as part of the therapeutic options for dealing with MDR-TB. There are also microbiological arguments to support the use of PAS in the management of the difficult-to-treat MDR-TB: it has *in vitro* activity on resistant strains, it does not share similar mechanism of action and resistance pattern with other available agents, providing rationale for its use as part of multi-therapy for treating MDR-TB.

Uncertainty in the knowledge about the beneficial effects

PD and efficacy

There is a lack of clarity regarding the PK/PD relationship of PAS but it is suggested that it is the time above MIC that is important for the bacteriostatic activity. PAS-GR should be administered to keep inhibitory concentrations above the MIC for most of the dose interval and Cmax should be targeted between 20-60µg/ml. With this in mind a posology of 4g, 8 to 12 hourly in adults would be suitable. To support this proposal, the applicant provided data from several PK studies (Peloquin 1994, 1999) and a more recent South- African Study (Liwa 2012). Overall, these data suggests that plasma concentrations would remain above the MIC for *M.tuberculosis* using a 4g bid regimen. A 4 g tid regimen, if tolerated, would be even a more secure approach. It guarantees higher exposure because of the higher variability in plasma concentrations observed with the bid regimen and also because accumulation of PAS occurs with the thrice daily regimen (median concentrations after one week of treatment was 28.5µg/ml) leading to sustained plasma concentrations of PAS. The 4g tid regimen is a close approximation of the dose used in the 'pivotal' study (BMRC 1950). An in-vitro dissolution study is provided in support of the current PAS formulation. In conclusion, the information provided is considered sufficient to support the proposed dose regimen in adult.

With regards to the paediatric population, 150mg/kg daily dose is proposed, based on data from the South African study which show that the PK parameter values obtained were not significantly different from what was observed in adults. However, no data are available in neonates and this is reflected in the SmPC.

Risks

Unfavourable effects

PAS was used in the latter part of the last century for the treatment of active tuberculosis, as part of a combination therapy. It would appear that the use of PAS diminished and was discontinued in many European countries due to its significant adverse gastro-intestinal side effects of nausea, vomiting and diarrhoea. PAS-GR has been developed with aim to reduce the gastro-intestinal side effects. It would also appear that cases of hypersensitivity, giddiness/vestibular symptoms, and jaundice have also been reported with the use of PAS.

Uncertainty in the knowledge about the unfavourable effects

In terms of exposure it is unclear how many people were exposed to PAS when it was commonly used. According to the applicant, a total of 781,359 packs of PAS-GR have been supplied to the US and other parts of the world between 1996 and 2010, which means approximately 10,000 patients, may have been exposed to it. From the information provided, PAS was used on a regular basis for more than 10 years from the first systematic and documented use in the EU and no safety concerns have been reported when PAS is used in combination with other medicinal products in the treatment of MDR-TB or XDR-TB, but this cannot be absolutely certain.

Benefit-risk balance

Importance of favourable and unfavourable effects

PAS has been shown historically to be beneficial when used as part of a treatment regimen for pulmonary tuberculosis. It has also been shown to reduce the emergence of resistant organisms to other anti-TB agents when used together. It was used widely in the past (1950s, 60s and 70s) but discontinued due to the significant gastro-intestinal side effects.

It is considered that PAS can make a contribution as part of a treatment regimen for MDR-TB or XDR-TB. It can be assumed that if the MIC for mycobacterium tuberculosis remains within the normal population distribution then PAS would contribute in the overall treatment regimen.

Para-aminosalicylic acid Lucane (PAS-GR) has been developed to reduce significant GI side effects and therefore could be potentially useful in adequate posology.

Benefit-risk balance

Overall, the benefit-risk is considered to be positive as it would appear that PAS is effective in the treatment of active tuberculosis and it also appears to reduce the incidence of resistant organisms. It is therefore considered that PAS can make a contribution as part of a treatment regimen for MDR-TB or XDR-TB with the assumption the MIC for mycobacterium tuberculosis remains within the normal population distribution. Furthermore, PAS has been included in WHO guidelines since 1997 and it is still included in the latest guidance for treatment of MDR-TB.

The CHMP concludes that PAS has been in well-established medicinal use within the Union, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I of Directive 2001/83/EC.

Discussion on the benefit-risk balance

PAS-GR is a gastro-resistant granular form of para-aminosalicylic acid (PAS), intended to treat multi-drug resistant TB (MDR-TB), which is defined as high-level resistance to both rifampicin and isoniazid with or without additional drug resistances and extensively-drug resistant TB (XDR-TB defined as MDRTB with resistance to a fluoroquinolone and at least one second line injectable agent). PAS-GR is to be used in combination with other agents to which the bacterial organism is sensitive.

For both MDR-TB and XDR-TB, it can be difficult to put together an adequate treatment regimen due to resistant organisms. Therefore it is considered that PAS-GR have a place in the treatment of MDR-TB/XDR-TB if an adequate dose is used, as it has been shown that PAS is effective in the treatment of

TB when used in combination with other anti-TB agents and also shown to reduce emergence of resistant strains.

4. Recommendations

Similarity with authorised orphan medicinal products

Not applicable

Derogation(s) from market exclusivity

Not applicable

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Para-aminosalicylic acid Lucane in the treatment of tuberculosis

"for use as part of an appropriate combination regimen for multi-drug resistant tuberculosis in adults and paediatric patients from 28 days of age and older when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see section 4.4).

Consideration should be given to official guidance on the appropriate use of antibacterial agents".

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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:

1. At the request of the European Medicines Agency;
2. 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 submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

None

- **Obligation to complete post-authorisation measures**

None

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable