HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
29 October 2014

GRANUPAS, gastro-resistant granules

30 sachets with a calibrated measuring spoon (CIP: 34009 278 801 5 5)

Applicant: LUCANE PHARMA

INN	para-aminosalicylic acid
ATC code (year)	J04AA01 (Drugs for treatment of tuberculosis)
Reason for the request	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123 2)
Indication concerned	**"GRANUPAS is indicated 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 "**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**Due to great need but poorly demonstrated efficacy in the treatment of MDR-TB, GRANUPAS (para-aminosalicylic acid) in combination with other TB medicines provides a minor improvement in actual benefit (level IV) in the treatment strategy for these patients.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	7 April 2014 (centralised procedure)
Prescribing and dispensing conditions/special status	List I Medicine for hospital prescription Orphan medicinal products (designation granted on 17 December 2010) Temporary authorisation for use by a cohort

ATC Classification	J	: Antiinfectives for systemic use
	J04	: Antimycobacterials
	J04A	: Drugs for treatment of tuberculosis
	J04AA	: Aminosalicylic acid and derivatives
	J04AA01	: 4-aminosalicylic acid

02 BACKGROUND

Historical background

This is an application for inclusion of a gastro-resistant form of an old tuberculosis medicine known under the name PAS, used from the 1940s. It was taken off the market in the 1960s after more effective tuberculosis medicines appeared.

Due to the appearance of multidrug-resistant tuberculosis, para-aminosalicylic acid (PAS) was put back into use in France by the Paris hospitals' central pharmacy in the 1980s. Then in 1994, PASER, the gastro-resistant form of para-aminosalicylic acid, was registered in the United States as an orphan drug.

In 2009, due to a supply shortage in the Paris hospitals' central pharmacy, PASER was used as a replacement medicine under a temporary authorisation for use by a named patient [ATU nominative in French] and then a temporary authorisation for use by a cohort.

Administrative background

The temporary authorisation for use by a cohort was granted on 8 February 2011 in the indication: "in adults in combination with several other known bactericidal or bacteriostatic antibiotics active on Mycobacterium tuberculosis in the treatment of multi-drug resistant tuberculosis (MDR-TB or XDR-TB) based on the results of susceptibility testing or when the use of isoniazid and rifampicin is impossible for reasons of cross-resistance or intolerance"

The medicinal product is sold globally under the name PASER In Europe, the EMA rejected this name due to a risk of confusion with another medicinal product. The initial Marketing Authorisation was obtained with the INN "para-aminosalicylic acid LUCANE" and the new name GRANUPAS was obtained on 15 May 2014.

03 THERAPEUTIC INDICATION

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

04 DOSAGE

"Adults
4 g (one sachet) three times per day.
The recommended schedule is 4 g every 8 hours. GRANUPAS can be taken with food.
Maximum daily dose is 12 g. Usual duration of treatment is 24 months.

Paediatric population
The optimal dose regimen in children is uncertain. Limited pharmacokinetic data suggest no substantial difference between adults and children.
For infants, children and adolescents the dosage will be adapted to the patient's weight at 150 mg/kg per day, divided in two intakes. A dosing spoon is provided to measure small doses below 4 g for young children.
The safety and efficacy of GRANUPAS in neonates have not been established. No data are available.

Desensitisation
Desensitisation can be accomplished by starting with 10 mg para-aminosalicylic acid given as a single dose. The dosage is doubled every 2 days until reaching a total of 1 gram after which the dosage is divided to follow the regular schedule of administration If a mild temperature rise or skin reaction develops, the increment is to be dropped back one level or the progression held for one cycle.
Reactions are rare after a total dosage of 1.5 g."

05 THERAPEUTIC NEED

Tuberculosis is a mycobacterium (Mbt) infection that most often affects the lungs. Globally, it remains a major cause of morbidity and mortality with high geographical and demographic disparities. Currently, France is considered to have a low incidence of tuberculosis with 5,187 cases reported in 2010.[1]

According to WHO,[2] multidrug resistant (MDR) tuberculosis is a mycobacterial infection resistant to isoniazid and rifampicin, the two major medicines for treating tuberculosis. It is called extensively resistant (XDR) when mycobacteria are also resistant to a fluoroquinolone class medicine and a second-line injectable TB medicine. Patients with XDR TB are included in patients with MDR TB.

Secondary or acquired resistance is caused by improper use of medicines (wrong prescription, poor compliance or low-quality medicine). The two main risk factors for resistance to TB medicines are treatment history and country of origin. MDR TB is especially common in Africa, Eastern Europe, Russia, China and India.

Resistance to TB medicines worsens the prognosis of the disease. Patients must be managed individually by specialised teams depending on the bacteriological findings and the patient's clinical features.

First-line TB medicines[3] (group 1) are rifampicin, isoniazid, pyrazinamide and ethambutol. In order to have a complementary effect on the different Mtb populations (intra or extracellular), several TB

[1] Antoine D. Les cas de tuberculose déclarés en France en 2010 . BEH 24-25, 12 June 2012. www.invs.sante.fr.
[2] WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update. www.who.int/tb. Website consulted on 10 September 2014.
[3] E.PILI, maladie infectieuses et tropicales . Edition 2011. Antituberculeux. p 72-74.

medicines must be combined in order to prevent the selection of resistant mutants and persistence of s low-metabolising bacilli.

According to WHO[2] guidelines, the principle for MDR TB treatment is to combine at least four active medicines of different groups (see Table 1) for an extended duration (≥ 18 months, 2 years in general). The choice of combined TB medicines will depend on the resistances.

Table 1: Second-line TB medicines, according to WHO (2011)

Group 2: injectable TB medicines	kanamycin amikacin capreomycin
Group 3: fluoroquinolones	levofloxacin moxifloxacin gatifloxacin ofloxacin
Group 4: oral bacteriostatic TB agents	ethionamide prothionamide cycloserine terizidone para-aminosalicylic acid
Group 5: other TB medicines	clofazimine linezolid amoxicillin/clavulanic acid thioacetazone clarithromycin imipenem

Medicines of WHO group 4 were being developed in 2011 (in phase III).

For treating MDR (including XDR) TB, WHO recommends combining pyrazinamide, a fluoroquinolone (preferably of the latest generation), an injectable TB medicine, ethionamide (or prothionamide) and cycloserine or para-aminosalicylic acid (PAS) when cycloserine cannot be used.

In order to prevent a therapeutic impasse in some cases of MDR TB, it is necessary to have enough second-line TB medicines to use in combination to be able to adjust the treatment in the event of contraindication or intolerance.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

No other medicinal product having a Marketing Authorisation in the treatment of MDR TB is available in France.

Bedaquiline (SIRTURO) from Jansen Cilag received a European Marketing Authorisation in 2014. However, the authorised 6-month pack size has not been validated by the ANSM [French National Agency for Medicines and Health Products Safety]. While awaiting a 1-month pack size, SIRTURO is available under a temporary authorisation for use by a cohort.

Other oral medicines are used off label, in combination according to the WHO guidelines (see Table 1 of section 05).

◗ Conclusion

There is no clinically relevant comparator available in France with a Marketing Authorisation in patients with MDR TB, but several other proprietary medicinal products are usable under a temporary authorisation for use or off label.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

PASER is available worldwide, with various statuses: authorised (especially in Europe, and the United States), in the process of registration or available under a humanitarian program.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

Proof of the efficacy of para-aminosalicylic acid (PAS) is mainly based on two efficacy trials published in 1950 and 1960.
No clinical trial has been done in the context of the current treatment of MDR TB with a combination of TB medicines.

8.1.1 MRC study of 1950

In 1950, the randomised study coordinated by the Medical Research Council[4] in the United Kingdom compared three treatment groups in 166 patients from ages 15 to 30 with bilateral pulmonary tuberculosis: 59 patients received streptomycin 1 g daily IM, 54 received PAS 20 g daily in four doses and 53 received a combination of streptomycin + PAS. The duration of treatment was 3 months.
An earlier trial conducted with a group of patients with the same characteristics that compared streptomycin with an untreated group (bed rest) on the same endpoints was used for the untreated group considered as a control.

This 1950 study did not comply with current good practice (for example, the patients were not informed of their participation in a clinical trial).

The primary endpoint was not defined in the 1950 publication. Many endpoints were evaluated for 6 months, including mortality, radiological progression and the percentage of negative sputum samples. There was no long-term analysis.
Statistically, the publication did not specify the calculations that were performed or the p values, but only the significance of the results.

In the 166 patients included, the severity of the tuberculosis measured by general condition, and the presence of fever and chest-x-ray cavities, was distributed evenly among the groups, most often severe or moderately severe.

The results presented are as follows:

- There was no difference in terms of mortality among the three groups.
- Radiological progression at 6 months was 56% of patients improved in the PAS group, 74% in the streptomycin group and 87% in the PAS + streptomycin group. In the untreated group from the earlier trial, 33% of untreated patients improved.
- Bacteriologically, the percentage of negative sputum cultures at 6 months (3 months after treatment discontinuation) was 8% in the PAS group, 19% in the streptomycin group and 33% in the PAS + streptomycin group.
- At 6 months, in patients with positive samples, streptomycin resistance appeared in the streptomycin + PAS group less often (5/48 or 10.4%), than in the streptomycin group (33/49 or 67%).

In conclusion, at the time, this study demonstrated the efficacy of PAS relative to no treatment, on radiological and bacteriological progression and the benefit of combination with another TB medicine on the appearance of resistance.

[4] Bignall J.R. Treatment of pulmonary tuberculosis with streptomycin and para aminosalicylic acid. British Medical Journal 1950, Nov11: 1073-85.

8.1.2 Study from the Madras tuberculosis treatment centre of 1960

In 1960, the WHO bulletin[5] published a randomised, double-blind study conducted by the Madras tuberculosis treatment centre in patients aged 12 years old or older with pulmonary tuberculosis. It compared four treatment groups: a group treated with PAS 10 g/day + isoniazid 400 mg/day in two doses and three groups treated by different dosages of isoniazid: 400 mg/day in one dose (ISN1), 400 mg/day in two doses (ISN2) and 200 mg/day in two doses (ISN3), for 12 months.

Patients included were older than age 12, including only two patients between 12 and 14, both in the PAS + ISN group. The severity of the disease was evaluated on general condition, weight, ESR, the existence of x-ray cavities and the extent of radiological lesions. These criteria were evenly distributed among the four groups except the frequency of tuberculosis cavities, which was less common in the PAS + ISN group than in the three other ones.
Statistically, the publication did not systematically specify the calculations that were performed or the p values.

The primary endpoint was not defined.

Among the 12-month results, the results of the comparison between the PAS + ISN group and the ISN2 group using the isoniazid dose of 400 mg are as follows:

- no significant difference was observed in terms of mortality.
- 85% of patients of the PAS + ISN group and 62% of the ISN2 group were radiologically improved.
- Sputum cultures were negative in 90% of patients of the PAS + ISN group and 51% of the ISN2 group.
- 86% of patients of the PAS + ISN group had strains sensitive to isoniazid versus 44% of the ISN2 group ($p < 0.01$).

In conclusion, at the time, this study demonstrated the greater efficacy of the PAS/isoniazid combination relative to isoniazid alone in radiological and bacteriological terms and on the appearance of resistance.

8.1.3 Other clinical trials

Other clinical trials were conducted with PAS before it fell into disuse. In these trials, PAS was combined variously with other TB medicines. They confirm the efficacy of a combination containing PAS and do not add anything to the two studies[4,5] presented above. They are presented for information purposes in the table of Appendix 1.

No clinical efficacy studies have been conducted in children. Only a few cases of children above age 12 were included in the studies.

08.2 Prescription data: TUA cohort

A temporary authorisation for use by a cohort was obtained in February 2011 in adults.

Between May 2011 and December 2013, 231 patients were included in this cohort at a rate of 70 cases per year. The patients included are men in 68% of cases, the median age is 36 and the disease was pulmonary only in 82% of cases.
The dose of GRANUPAS used was 12 g per day in 52% of cases (recommended dose); it was less in the other cases. The mean treatment duration is 1 year.

[5] Tuberculosis Chemotherapy Centre, A Concurrent Comparison of Isoniazid plus PAS with Three Regimens of Isoniazid Alone in the Domiciliary Treatment of Pulmonary Tuberculosis in South India. Bull. WHO 1960

All the patients included in the cohort were resistant to isoniazid and rifampicin, except in 7 cases where they were resistant to one of the medicines and intolerant of the other. Furthermore, resistance or intolerance to at least one other TB medicine was reported in 146 cases (63%).

Two cases of resistance to para-aminosalicylic acid were found, while 57 patients were resistant to at least one of the other three group 4 TB medicines (see section 05), that is, ethionamide, cycloserine or linezolid.

The prescriptions were associated with other TB medicines according to the Marketing Authorisation recommendations. The most common combinations were:

GRANUPAS + amikacin + moxifloxacin	108 patients
GRANUPAS + amikacin + moxifloxacin + linezolid	54 patients
GRANUPAS + amikacin + moxifloxacin + linezolid + cycloserine	36 patients

08.3 Safety/Adverse effects

8.3.1 Old safety data with PAS

Between 1946 and the 1960s, tuberculosis was common and PAS widely used in combination with isoniazid and streptomycin in order to reduce resistance. The adverse effect profile for PAS was known, with the common and sometimes intense gastrointestinal effects being pre-eminent (nausea, vomiting, diarrhoea, abdominal pain, etc.). This is why various preparations have been developed with the goal of reducing these gastrointestinal effects.

In the two clinical trials presented above[4,5] the main effects were also nausea, diarrhoea, vomiting, as well as rash and pruritus. In the MRC trial of 1950, gastrointestinal effects were found between 51% and 58% in the groups receiving PAS. They were not calculated in the study by the Madras tuberculosis treatment centre of 1960.

During its use, cases of liver damage of greater or lesser severity (hepatitis, cytolysis) have been reported; no deaths have been reported due to an adverse effect.

The GRANUPAS gastro-resistant granulate form was developed to delay the release of PAS and its breakdown into meta-aminophenol, which is responsible for the gastrointestinal effects.

The applicant has provided safety studies in healthy volunteers with GRANUPAS that found these gastrointestinal effects, but it is not possible to directly compare their intensity relative to the effects induced by older PAS formulations.

8.3.2 Recent data with GRANUPAS

According to the SPC, analysis of all the available studies conducted with GRANUPAS showed gastrointestinal effects in 26% of cases (nausea, vomiting, diarrhoea, abdominal pain, bloating, etc.), hypersensitivity reactions in 6.3% of cases, nervous system effects in 6.1% of cases (vertigo, headache, dizziness, visual disturbances, peripheral neuropathies, tendon pain) and liver abnormalities in 2.1% of cases (cytolysis, decreased prothrombin level, increased alkaline phosphatase and serum transaminases).

Among the 231 patients included in the temporary authorisation for use scheme, there were 15 treatment discontinuations for adverse effects. These effects are not all attributed to GRANUPAS No serious adverse effect was reported during this follow-up.

For patients whose treatment discontinuation and the reason for it were reported, the reasons for treatment discontinuation were as follows:

Table 1: Reason for treatment discontinuation

Reasons	N	%
Recovery	16	29
Side effect	15	27
Lack of efficacy	4	7
Patient choice	3	5
Lost to follow-up	5	9
Death	0	0
Not specified	12	22
Total	55	100.0

It is difficult to analyse the reasons for discontinuing treatment, whether in terms of safety or efficacy, because GRANUPAS was used in combination with other TB medicines in a non-comparative cohort and there is nothing to tell us what role each medicine played.

8.3.3 Data in children

In France between 2011 and 2013, 11 children received this medicine under a temporary authorisation for use by a named patient. No serious adverse event was reported.

08.4 Summary & discussion

The efficacy of GRANUPAS relies essentially on previous experience:

- Extensive use of aminosalicylic acid between 1946 and the 1960s, during which the medicine was gradually abandoned due to the appearance of more effective treatments.
- Mainly two clinical trials published in 1950 and 1960, which, with the required methodology of the time, showed the efficacy of PAS relative to no treatment, the benefit of combining PAS with another TB medicine and the benefit of this combination to reduce resistance.
  These two trials were conducted in pulmonary tuberculosis in patients who were not resistant to TB medicines, with a treatment duration of 3 months and 6 months. These studies do not comply with current methodological requirements.

There is no clinical trial showing the efficacy of GRANUPAS in its current indication of MDR TB, in combination with at least four TB medicines and a treatment duration of at least 18 months.

Furthermore, there is a non-comparative French cohort of 231 patients followed as part of a temporary authorisation for use by a cohort during which GRANUPAS was used in combination with at least two other TB medicines. In 63% of cases, the strains were resistant to at least one other TB medicine besides rifampicin and isoniazid, 55 out of 231 patients discontinued treatment, but the reasons for discontinuation could not be interpreted in terms of efficacy or safety. No serious adverse effects were reported. The Committee is regretful that the data from the TUA cohort were not better exploited.

In terms of safety, the most common adverse effects are nausea, vomiting, diarrhoea, abdominal pain and bloating, which can sometimes be significant. The current gastro-resistant formulation is designed to be better tolerated, but the effects persist and we do not know if their intensity has decreased. Hepatocytolysis and abnormal lab values were observed. No serious adverse effects were observed either in the past or in the more limited current use.

Clinical experience in children is limited to a few cases in the old studies and to 11 cases under a temporary authorisation for use by a named patient in which no serious adverse effects were attributed to GRANUPAS.

09 THERAPEUTIC USE

Treatment of MDR (including XDR) TB is specified by WHO[2] depending on the extent of resistance suspected, or detected with susceptibility testing. This varies depending on the country, the usual management of tuberculosis in this country and the treatment already received by the patient.

PAS is a bacteriostatic TB medicine; it has the benefit of limiting the appearance of resistance to the bactericidal TB medicines with which it is combined.

In Europe, PAS is indicated for use in combination with other TB medicines 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

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ MDR TB is a rare disease in France and frequently fatal. Its frequency, stable in France, has risen sharply worldwide.

◗ This proprietary medicinal product is intended as curative therapy.

◗ The safety of GRANUPAS is good despite frequent nausea, vomiting, diarrhoea, etc., but the proof of its efficacy relies mainly on old data that do not correspond to the current indication. The efficacy/adverse effects ratio for this medicinal product is modest.

◗ There is no treatment alternative available in France with a Marketing Authorisation in MDR TB; however, other products with a temporary authorisation for use or used off label may be used.

◗ This medicinal product is a second-line therapy for MDR TB.

◗ Expected public health benefit:

In France, the burden of tuberculosis is low to moderate, representing, according to WHO (2004 data), 4 per 100,000 age-standardised DALYs; tuberculosis is classified in Europe (WHO 2010 projection) in just 107th place among the causes of DALYs. The burden of MDR TB remains low, given the limited number of patients concerned in France.

In France, although the number of cases of TB has been gradually decreasing since the 1970s, it remains high in some regions and for some population groups. Also, fighting tuberculosis remains a public health priority, established in the National Tuberculosis Programme 2007-2009 developed under the public health act of 2004 and its 100 objectives.

In view of the available data (data from very old trials, that do not comply with current standards and data from non-comparative temporary authorisation for use by a cohort, the impact of GRANUPAS on morbidity and mortality in the patients treated cannot be quantified. The impact on quality of life is not documented. GRANUPAS is not expected to have any impact on the organisation of healthcare.
The transferability of the study data to current clinical practice is poor.

GRANUPAS is a partial response to the identified public health need, by better management of some patients with MDR TB.

However, particularly due to the very low number of patients concerned, it is not expected that GRANUPAS will impact public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of GRANUPAS is substantial in the Marketing Authorisation indication.

The Committee recommends inclusion of GRANUPAS on the list of medicines approved for hospital use in the indication "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" and at the dosages of the Marketing Authorisation.

010.2 Improvement in Actual Benefit (IAB)

Due to great need but poorly demonstrated efficacy in the treatment of MDR-TB, GRANUPAS (para-aminosalicylic acid) in combination with other TB medicines provides a minor improvement in actual benefit (level IV) in the treatment strategy for these patients.

010.3 Target population

In France,[6] the frequency of MDR TB in a population who have already received a TB treatment is 9%. It is 1% in the untreated TB population. In 2008-2009, the number of cases was around 50 cases of MDR TB per year and 0 to 4 XDR TB cases per year.
In France, between 2011 and 2013, the number of patients included under a temporary authorisation for use by a cohort remained stable every year at between 70 and 80 patients. However, the number of MDR TB cases worldwide is increasing and an increasing number of cases in France is possible.

The target population is therefore at least 70 to 80 patients a year.

[6] Veziris N, La résistance aux antituberculeux en France en 2009-2010, BEH 24-25, 12 June 2012, www.invs.sante.fr.

APPENDIX 1
Summary of the results of efficacy studies in clinical trials (according to the EMA[7])

Author reference	Number of patients that could be evaluated	Objective	Method	Results
Selkon[8] India	See Madras pivotal study	Evaluate the emergence and degree of ISN resistance	Post hoc analysis of the 1960 Madras clinical trial Only the PAS + ISN vs ISN monotherapy groups	Resistant strains 16 in the PAS + ISN group vs 57 in the ISN monotherapy group
Lotte A [9] India	150 patients ISN + STP 79 ISN + PAS: 71	Evaluate a continuous vs an intermittent treatment	Strictly supervised vs unsupervised treatment Administration three times a week vs every day of ISN 650 mg + STP 1 g IM vs ISN 200 mg + PAS 0.2-0.3 g/kg/day or 10 g per day Duration 12 months	Multiple comparisons not usable for efficacy analysis
Dawson[10] India	220 patients ISN + PAS: 72 ISN + TATZ: 77 ISN + PAS (2 steps): 71	Evaluate the different combinations in outpatient treatment	ISN 4.5 mg/kg/day + PAS 0.22 mg/kg/day vs ISN 6.9 mg/kg/day + TATZ 3.4 mg/kg/day vs ISN 5.5 mg/kg/day + PAS 1.7 mg/kg/day For 6 months followed by ISN 6.78 mg/kg/day Duration 12 months	Multiple comparisons not usable for efficacy analysis
Dawson[11] India	193 patients Outpatients: 96 Sanatorium: 97	Compare inpatients with outpatients for 5 years	ISN 0.2-0.3 g/kg + PAS 4-6 mg/kg/day for 12 months Then ISN 4-6 mg/kg/day vs placebo	Efficacy at 12 months between 73% and 86%
Ramakrishnan[12] 1969 India	119 patients ISN + STP: 66 ISN + PAS: 53	Compare the efficacy of two treatment protocols for 4 years.	high dose ISN 12.5 mg/kg/day + STP 1 g IM twice weekly vs ISN 4.4 mg/kg/day + PAS 0.22 g/kg/day for 12 months	ISN + STP: eight treatment failures/three new treatments ISN + PAS:

[7] EMA, Assessment report, GRANUPAS, 26 November 2013, www.ema.europa.eu.

[8] Selkon JB, Tuberculosis Chemotherapy centre Madras Bull Wld Hlth Org. 1964; 31: 273-94.

[9] Lotte A, A concurrent comparison of intermittent (twice-weekly) isoniazid plus streptomycin and daily isoniazid plus PAS in the domiciliary treatment of pulmonary tuberculosis; Tuberculosis Chemotherapy centre, Madras. Bull Wld Hlth Org. 1964; 31: 247-271.

[10] Dawson JJ. Isoniazid plus thioacetazone compared with two regimens of isoniazid plus PAS in the domiciliary treatment of pulmonary tuberculosis in South Indian patients. Chemotherapy centre Madras. Bull Wld Hlth Org. 1966; 34: 483-15.

[11] Dawson JJ. A 5-year study of patients with pulmonary tuberculosis in a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. Chemotherapy centre Madras Bull World Health Organ. 1966; 34(4): 533-51.

[12] Ramakrishnan CV. A four-year follow-up of patients with quiescent pulmonary tuberculosis at the end of a year of chemotherapy with twice-weekly isoniazid plus streptomycin or daily isoniazid plus pas Tubercle. Diabetes Care. 1969 Jun; 50(2): 115-24.

			Then ISN 400 mg for 12 months or 300 mg for 6 months vs placebo	eight treatment failures/five new treatments one death
Tuberculosis Chemotherapy centre Madras[13] India	415 patients (359 analysed) ISN + STP: 181 *vs* ISN + STP + PAS: 178	Compare two treatment combinations ISN + STP 1 g or ISN + STP 0.75 vs ISN + STP 1 g + PAS or ISN + STP 0.75 + PAS	ISN 400 mg/day for 1 month followed by 13-17 mg/kg/day + STP 1 g/day (or 0.75 g/day) vs the same combination plus PAS 6 g/day Duration 12 months	Bacteriological response: Equivalent treatments with 85% favourable response vs 87% Clinical response: ISN + STP: two deaths and four radiological exacerbations ISN + STP + PAS: no deaths or exacerbations ISN resistance: 8% vs 5%
British Medical Research Council[14] UK	481 patients (412 analysed) ISN + STP + PAS: 109 ISN + STP + EMB: 97 ISN + STP + RMP: 103 ISN + STP + PAS followed by high dose ISN + STP: 103	Evaluate the efficacy of four different dosage regimens	ISN + STP + PAS 12 g/day ISN + STP + EMB ISN + STP + RMP ISN + STP + PAS followed by high dose ISN + STP Duration of triple combination: 3 months Additional 9-month treatment	The AARB elimination rate in sputum was equivalent in the four groups and significantly higher in the RFP group. At 12 months, 96% of patients treated with PAS had a favourable bacteriological response.
Tuberculosis Chemotherapy centre Madras[15] India	247 patients (173 analysed) ISN + PAS twice weekly: 122 (90 analysed) ISN + PAS every day: 125 (83 analysed)	Compare a strictly supervised treatment with a self-administered treatment	STP 1 g/day + ISN 400 mg/day + PAS 6 g/day for 2 weeks: then randomisation - either ISN 15 mg/kg/day + PAS 0.2 g/kg twice weekly - or ISN 4.7 mg/kg/day + PAS every day: 0.2 g/kg/day	Equivalent efficacy at 12 months 88% vs 87% had a favourable bacteriological response

1 PAS: para-aminosalicylic acid sodium / STP: streptomycin / ISN: isoniazid / TATZ: thioacetazone / EMB: ethambutol / RMP: rifampicin
2 AARB: acid-alcohol resistant bacilli

[13] Chemotherapy centre Madras A controlled comparison of two fully supervised once-weekly regimens in the treatment of newly diagnosed pulmonary tuberculosis. Tubercle. 1973 54(1): 23-45.
[14] Co-operative controlled trial of a standard regimen of streptomycin, PAS and isoniazid and three alternative regimens of chemotherapy in Britain. A report from the British Medical Research Council. Tubercle. 1973 54: 99-129.
[15]. Tuberculosis Chemotherapy centre Madras. Controlled comparison of oral twice-weekly and oral daily isoniazid plus PAS in newly diagnosed pulmonary tuberculosis. Br Med J. 1973 7; 2 : 7-11