Acute Lymphoblastic Leukaemia
PI ALL-2 Protocol

(PI ALL-2 does not replace PI ALL-1, which will continue to be used in some countries. PI ALL-2 is for those countries resourced for a more intensive regimen)

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TREATMENT OUTLINE

Prephase (phase 0, 1 week)

IT MTX, Prednisone.

Induction (phase 1, 4 weeks)

IT MTX, Prednisone, Vincristine, L-Asparaginase

CNS prophylaxis/Consolidation (phase 2, 6 weeks)

IT MTX, Cyclophosphamide, ARA-C, 6-Mercaptopurine

Interim Maintenance (phase 3, 8 weeks)

IT MTX, Vincristine, Dexamethasone, 6-Mercaptopurine, Methotrexate

Delayed Intensification (phase 4, 8 weeks)

IT MTX, Vincristine, Dexamethasone, Doxorubicin, L-Asparaginase, Cyclophosphamide, ARA-C, 6- Mercaptopurine

Continuous Maintenance (phase 3, 84 weeks)

IT MTX, Vincristine, Dexamethasone, 6-Mercaptopurine, Methotrexate

Note: IT MTX for first year of therapy only

Abbreviations:

VCR = vincristine; PDN = prednisone; L-asp = L-asparaginase;
Cyclo = cyclophosphamide; Ara-C = cytarabine; MTX = methotrexate;
ITMTX = intrathecal methotrexate; 6MP = 6-mercaptopurine;
DEX = dexamethasone;

1.0 AIMS

1.1 Primary

To increase the proportion of children with acute lymphoblastic leukaemia (ALL) who are cured.

1.2 Secondary

To assess the ability of Pacific Island health systems to deliver chemotherapy according to an adapted protocol.

To assess the ability of Pacific Island health systems to provide supportive care guided by protocol and shared care consultation from NZ centres.

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2.0 RATIONALE FOR STUDY DESIGN

Children and young people in the Pacific have not enjoyed the survival of their peers in developed health systems. This has been the result of a number of factors including late or non diagnosis, treatment toxicity on protocols considered standard in developed health systems and treatment abandonment due to expense and family dislocation. This protocol has been drawn from strategies used by NZ and Australian paediatricians to treat children with ALL in the past, at a time when the ability to treat and support children with malignant disease was at an early stage of development.

The protocol should be able to be delivered in its entirety in Fiji. Eligible patients in Samoa and Tonga will receive prephase in their base hospital and will then be referred to NZ for Induction and CNS prophylaxis/consolidation. All patients will be repatriated for on going therapy (or palliative care if not achieving remission)

The production of the ALL-2 protocol acknowledges that capability for supportive care has increased and that treatment related mortality and abandonment of therapy have declined. This has enabled the addition of a delayed intensification phase to the ALL-1 protocol and this more intensive regimen should result in a higher survival rate for children with ALL, albeit with a greater need to monitor for and deal with toxicity.

The ALL-2 protocol incorporates the recommendations made in the Paediatric Blood and Cancer paper of 2009 by Hunger, Sung and Howard. (Regimen 2/3 delayed intensification is used directly as written) It should be noted that the PI ALL-1 protocol contained consolidation which is similar to Regimen 3, but it has been changed in PI ALL-2 to come into line with Regimen 3. This involves changing timings and omitting Vincristine)

In keeping with increasing capability for supportive care, the 6-mercaptopurine dosages have been increased to those in current general usage (as recommended in the 2009 paper). The intent is to make anti-metabolite dose more intensive with adjustments made to individual patient tolerance.

There is no prephase in the 2009 Hunger et al paper. However, this allows time for response assessment and logistic arrangements for Pacific patients and has been left unchanged from the ALL-1 protocol. Because of the increased intensity of the ALL-2 protocol, failure to clear blasts from the peripheral blood at day 8 is no longer a contraindication to proceeding with protocol therapy, though it must be acknowledged that these patients will be at higher risk of relapse.

3.0 PATIENT ELIGIBILITY

3.1 Newly diagnosed children with ALL aged between 1 and 18 years of age (inclusive) without B-cell ALL (FAB L3) are eligible.
3.2 Patients with Down syndrome.
3.3 Patients who are not in remission on the Day 29 BMA come off protocol and receive symptomatic care.

4.0 EXCLUSIONS

4.1 Patients with B-cell ALL [FAB L3]
4.2 Patients aged ≤ 1 year or ≥ 18 years at diagnosis
4.3 Patients with CNS disease (CNS blasts > 5 $x10^6$/L) are not eligible

5.0 INITIAL EVALUATION

5.1 Complete history including family history
5.2 Complete physical examination including careful documentation of size of lymph nodes, spleen and liver size, presence of extra-medullary involvement (eg, eyes, testes in boys)
Measure height and weight and calculate surface area
5.3 Chest X-ray
5.4 Full blood and platelet count
5.5 Bone marrow aspirate (BMA)/trephine
5.51 For morphology and cytochemistry
5.6 CSF examination
5.61 For cell count
5.62 For cytospin
5.7 Biochemistry
(liverfunction/urea,electrolytes,creatinine,urate,calcium,phosphate),
cultures, mantoux, virology (Hepatitis B) etc according to clinical circumstances and individual institution's requirements. Note a negative mantoux does not exclude Tb

6.0 REGISTRATION

6.1 Upon diagnosis all patients with ALL will be recorded on the unit registry.

7.0 TREATMENT

All eligible patients receive identical therapy. CNS preventative therapy will vary according to age. Total length of therapy is 102 weeks (2 years) from documentation of remission (see 7.5).

7.1 Stabilisation

Induction therapy should not commence until appropriate supportive care has been given. This includes correction of anaemia and thrombocytopenia, treatment of infection, appropriate hydration, allopurinol and correction of electrolyte disorders.
A suggested routine is - allopurinol 300 mg/m2/day in 3 divided doses - Hydration at 3000mL/m2/day (125mL/m2/hour) with 4% Dextrose and 1/5 N Saline, initially potassium free. Individual institutions may have different concentrations dextrose saline (3.5% dextrose/1/3 N saline)

7.2 Referral to NZ

For patients in Samoa and Tonga, initiate proceedings for referral to NZ at day 8

7.3 Prephase with prednisone and ITMTX

PREPHASE- 1 WEEK
All eligible patients will begin prednisone prephase after confirmation of diagnosis on bone marrow aspiration and following lumbar puncture and administration of age appropriate dose of intrathecal methotrexate.

7.31 Prednisone 40 mg/m2/day orally in 2 divided doses Days -7 to 0

7.311 Hyperglycaemia - no modification will be made and insulin therapy will be used

7.312 Hypertension - reduce dose by 50% and consider sodium restriction and anti-hypertensives

7.313 Pancreatitis - if severe, cease

7.32 Intrathecal methotrexate on Day-7

7.321 Methotrexate will be administered according to an age-related formula:

Age	1-2 years	2-3 years	>3 years
Dose	8mg	10mg	12mg

Perform lumbar puncture and if CSF flowing freely collect 4-5 mls and send CSF for cytospin and a smaller volume for culture.

If CSF blood stained this makes analysis difficult due to blood contamination. May need to resite needle. Inject IT methotrexate as a slow push. There should be no resistance.

Patients with differential lymphoblast counts less than $1x10^9$/L on day 8 are regarded as good responders.

In Fiji, patients will proceed to induction. In Samoa and Tonga, patients will be sent to New Zealand.

7.4 Induction Therapy

INDUCTION THERAPY - 4 WEEKS

Induction to follow on directly after the prephase.

During induction therapy no dose will be delayed **solely** because of myelosuppression.

7.41 Vincristine 1.5mg/m^2 (maximum dose 2mg) IV push on Days 1, 8, 15 and 22.

7.411 Seizures secondary to vincristine - withhold one dose then reinstitute (on anticonvulsant therapy).

7.412 Severe foot drop, paralytic ileus - withhold dose and resume at 1.0 mg/m^2. When symptoms abate, escalate to full dose as tolerated.

7.413 Jaw pain - treat with analgesics and do not modify vincristine dose.

7.414 Defer if abnormal liver function is present (AST >3x upper limit of normal or bilirubin >25 μmol/L). Resume when liver function is returning to normal.

7.42 Prednisone 40 mg/m^2/day orally in 2 divided doses on days 1-22 and then stopped without taper.

7.421 Hyperglycaemia - no modification will be made and insulin therapy will be used.

7.422 Hypertension - reduce dose by 50% and consider sodium restriction and anti-hypertensives.

7.423 Pancreatitis - if severe, cease.

7.43 E coli (LEUNASE) L-asparaginase 6000 U/m^2 IM x 9 doses on Monday, Wednesday, Friday starting on Day 2 or 3.

7.431 Hyperglycaemia - no modification will be made and insulin therapy will be used.

7.432 Pancreatitis - if symptomatic and hyperamylasaemia is present (> 2.6x upper limit of normal), L-asparaginase should be ceased and not restarted.

7.433 Bleeding (not due to thrombocytopenia) or thrombosis - withhold L-asparaginase until resolved. Laboratory evidence alone of abnormal haemostasis without bleeding is not an indication to withhold L-asparaginase.

7.434 Allergy or anaphylaxis. If objective hypersensitivity to E. coli L-asparaginase occurs, international

practice would be to substitute Erwinia asparaginase However because of the extremely high cost of this product it will not be available for use by Pacific Island health systems. In this eventuality Asparaginase administration would cease with allergy to E coli Asparaginase (Leunase).
Pain and non-allergic inflammation are <u>not</u> an indication to withhold L-asparaginase.

7.435 Stroke syndrome or cerebral thrombosis or haemorrhage are indications to cease L-asparaginase.

7.436 Individual institutions may wish to monitor clotting profiles during L-asparaginase therapy. However, abnormal results without clinical manifestations are not an indication to withhold L-asparaginase.

7.44 Intrathecal Methotrexate Days 15 and 29

Age	1-2 years	2-3 years	> 3 years
Dose	8 mg	10mg	12mg

7.441 Omit if renal failure present and substitute cytarabine (ARA C)

7.442 Omit if Grade 3 or 4 stomatitis (ulcers and liquid diet only or alimentation not possible) and substitute Ara-C.

7.443 Intrathecal dose of Ara-C

Age	1-2 years	2-3 years	> 3 years
Dose	20 mg	24 mg	30mg

7.444 Patients with a CSF white cell count of $<5 \times 10^6$/L but with unequivocal lymphoblasts on cytospin will receive additional intrathecal methotrexate on days 8 and 22.

7.5 Documenting Remission

Documentation of Remission

A bone marrow aspirate will be performed on Day 29, along with an Intrathecal dose of Methotrexate. If marrow is in remission (M1) proceed with next phase on Day 36. Remission is defined as a normocellular marrow with <5% blasts present. Any patient who fails to achieve remission on day 29 will be off protocol.

7.51 Therapy is given for 102 weeks (2 years) from documentation of remission

8.0 CNS PREVENTATIVE - CONSOLIDATION THERAPY 6 WEEKS

CNS preventative - consolidation therapy commences provided the patient is in remission and the absolute neutrophil count is $>0.5 \times 10^9$/L and the platelet count is $>80 \times 10^9$/L. Once begun the first 14 days of chemotherapy will be given without interruption, unless life threatening complications are present (this will almost always only be sepsis). The second phase due on Day 22 should only be commenced if the absolute neutrophil count is $>0.5 \times 10^9$/L and the platelet

count >80 x10^9/L. Once commenced this pulse should only be interrupted for life threatening complications.
Commence *Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole (see appendix A1.1).

8.1 CNS prevention

8.11 Intrathecal Methotrexate Days 1, 8 and 15

All patients receive intrathecal methotrexate in age related doses

Age	1-2 years	2-3 years	> 3 years
Dose	8 mg	10mg	12mg

Send CSF for cytospin.

8.2 Consolidation

8.21 Cyclophosphamide 1000 mg/m^2 IV on Days 1 and 22 (see appendix A1.2).

8.211 Gross haematuria - consider using mesna with subsequent doses.

8.212 Microscopic haematuria - add frusemide to IV fluid regimen and continue IV fluids for at least 24 hours.

8.213 Remember that the second dose of cyclophosphamide commencing on Day 22 (and the Ara-C {see 8.221}) should only be given if the nadir has been passed and the absolute neutrophil count is >0.5 x10^9/L and the platelet count >80 x10^9/L.

8.22 Ara-C 75 mg/m^2/day subcutaneously on Days 1-4, 8-11, and 22-25, 29-32

8.221 The dose due on Day 22 at the time of the second dose of cyclophosphamide (see 8.213) should only be given if the nadir has been passed and the absolute neutrophil count is >0.5 x10^9/L and the platelet count >80 x10^9/L.

8.222 Withhold if bilirubin >25 umol/L or transaminases >2.5x upper limit of normal (grade 3 hepatotoxicity).

8.223 Do not modify for rash.

8.23 6 Mercaptopurine 60mg/m2 oral days 1-28 (refer table page 14 for dosage)

8.231 Neutropenia is expected during this phase as a result of Cyclophosphamide and Ara-C therapy and 6MP will not be ceased or reduced except for life threatening sepsis.

8.232 6MP is given once daily at bed time and without food or milk products. If vomiting occurs within 2 hours the full dose should be repeated

9.0 INTERIM MAINTENANCE – 8 weeks

This phase of treatment, identical to the later continuation therapy, provides time to recover from Consolidation phase. Interim Maintenance therapy only commences if the absolute neutrophil count is >1.0 $x10^9$/L and the platelet count >100 $x10^9$/L. Blood counts should be done at least once every 28 days (ie with each VCR) or more frequently if dose adjustment of 6MP is necessary (see 9.32 to 9.35). Liver function tests (LFT's) are recommended every 8 weeks or more frequently if clinically indicated.

Continue trimethoprim-sulfamethoxazole prophylaxis.

9.1 Vincristine 1.5mg/m^2 IV (maximum dose 2mg) every 28 days (see 7.41).

9.11 Vincristine and the 5 day pulse of dexamethasone are to be given together every 28 days irrespective of blood count (see 9.21).

9.2 Dexamethasone 6mg/m^2/day orally for 5 days every 28 days in 2 divided doses

9.21 Dexamethasone and the IV push of vincristine are to be given together every 28 days irrespective of blood counts (see 9.11).

9.3 6-mercaptopurine 75mg/m^2/day continuously for 8 weeks

9.31 6MP is given once daily at bed time and without food or milk products. If vomiting occurs within 2 hours the full dose should be repeated. The aim is to give 350 mg/m^2/week as shown in the table page 17.

9.32 An FBC is performed every 28 days prior to each vincristine and dexamethasone pulse. If the neutrophil count drops to between 0.5-1.0$x10^9$/L and/or the platelet count to 50-100 $x10^9$/L then both 6-mercaptopurine and methotrexate should be reduced by 25%. The count should then be repeated at weekly intervals.

9.33 When counts recover to neutrophils >1.0$x10^9$/L and platelets >100$x10^9$/L then resume therapy at standard dose.

9.34 If the neutrophil count is <0.5$x10^9$/L and/or the platelet count <50$x10^9$/L then oral 6-mercaptopurine and methotrexate are ceased. Upon recovery to neutrophils >1.0 and platelets >100 therapy is resumed at 50% of standard doses and increased to 75% and 100% as tolerated. (This will usually be at 2 week intervals).

9.35 There is no dose escalation above 75mg/m^2/day during this phase irrespective of counts

9.4 Methotrexate 20 mg/m^2 orally weekly

Oral methotrexate is given in the evening together with 6-mercaptopurine (see 9.31) –refer table on page 16.

9.41 Grade 2-4 nephrotoxicity (creatinine >2.6x upper limit of normal) - omit until toxicity resolved (Grade 0, creatinine <1.25x upper limit of normal).

9.42 Grade 3-4 hepatotoxicity - omit until Grade 0-2 toxicity then resume at half dose. Escalate dose at 2 weekly intervals, provided Grade 3-4 toxicity does not recur.

9.43 Grade 2 stomatitis (erythema, ulcer, can eat solids) of >3 days duration, decrease dose by 30%. Grade 3-4 stomatitis - withhold until resolved and resume dose at 50%.

9.44 The dose of oral methotrexate due on the week of intrathecal methotrexate is withheld.

9.45 Dose guidelines for methotrexate:
An FBC is performed every 28 days prior to each vincristine and dexamethasone pulse. If the neutrophil count drops to between 0.5-1.0x10^9/L and/or the platelet count to 50-100 x10^9/L then both 6-mercaptopurine and methotrexate should be reduced by 25%. The count should then be repeated at weekly intervals.

9.46 When counts recover to neutrophils >1.0x10^9/L and platelets >100x10^9/L then resume therapy at standard dose.

9.47 If the neutrophil count is <0.5x10^9/L and/or the platelet count <50x10^9/L then oral 6-mercaptopurine and methotrexate are ceased. Upon recovery to neutrophils >1.0 and platelets >100 therapy is resumed at 50% of standard doses and increased to 75% and 100% as tolerated. (This will usually be at 2 week intervals).

9.48 There is no dose escalation above 20mg/m^2/day during this phase irrespective of counts

9.5 IT MTX Day 29

All patients receive intrathecal methotrexate in age related doses

Age	1-2 years	2-3 years	> 3 years
Dose	8 mg	10mg	12mg

Send CSF for cytospin

10. DELAYED INTENSIFICATION

This therapy is intensive and needs close surveillance for toxicity. The frequency of the IV therapy and the need for close surveillance means the patient should be close to the treatment centre throughout this phase.

Consider the insertion of central venous access for this phase (eg. PICC line)

Note that the day this phase should only be started if the absolute neutrophil count is >1.0 x10^9/L and the platelet count >100 x10^9/L.

Once begun, it should **continue without interruption until Day 29**

At day 29, treatment should only be started if the absolute neutrophil count is >1.0 x10^9/L and the platelet count >100 x10^9/L.

10.1 Vincristine 1.5mg/m^2 IV (maximum dose 2mg) days 1, 8, 15

10.11 Vincristine is to be given regardless of count. (see 7.41).

10.2 Dexamethasone 10mg/m^2/day orally in 2 divided doses, days 1-7 and 15-21

10.3 Doxorubicin 25 mg/m^2 IV Days 1, 8, 15

10.31 Doxorubicin is to be given regardless of count.

10.32 Doxorubicin is given as a slow IV push with the same precautions as for Vincristine

10.4 E coli L-asparaginase (LEUNASE) 6000 U/m^2 IM x 6 doses on Monday, Wednesday, Friday starting at Day 3

10.41 See **7.431, 7.432, 7.433,**

10.42 See **7.434** Allergy or anaphylaxis. If objective hypersensitivity to E.coli L-asparaginase occurs, international practice would be to substitute Erwinia asparaginase. However because of the extremely high cost of this product will not be available for use by Pacific Island health systems. In this eventuality Asparaginase administration would cease with allergy to E coli Asparaginase (Leunase). Pain and non-allergic inflammation are <u>not</u> an indication to withhold L-asparaginase.

10.5 Cyclophosphamide 1000 mg/m^2 IV on Day 29

10.51 Need absolute neutrophil count >1.0 x10^9/L and platelet count >100 x10^9/L to start day 29 therapy (See **8.211, 8.212)**

10.6 Ara-C 75 mg/m^2/day subcutaneously on Days 29-32 and 36-39

10.7 6-mercaptopurine 60mg/m^2/day once daily, days 29-43 (refer table page 16 for dosage)

10.71 Neutropenia is expected during this phase as a result of Cyclophosphamide and Ara-C therapy and 6MP will not be ceased or reduced except for life threatening sepsis

10.8 IT MTX Days 1, 29, 36

All patients receive intrathecal methotrexate in age related doses

Age	1-2 years	2-3 years	> 3 years
Dose	8 mg	10mg	12mg

Send CSF for cytospin.

11.0 CONTINUATION THERAPY - 84 weeks

This therapy continues provided complete continuous remission is maintained until 2 years of therapy, from the time of documentation of remission, (see 7.5) has been given.

Need to ensure a regular supply of medication and need to emphasise the importance of compliance. Aim is to avoid where possible interruptions in therapy. Dose reduction may be needed due to cytopaenia but uninterrupted therapy at a lower tolerable dose better than interrupted chemotherapy at protocol doses. If neutrophil counts are consistently high despite increasing doses, check lymphocyte count. If >1.5 suspect non-compliance as an explanation.

CONTINUATION

Continuation therapy only commences if the absolute neutrophil count is >1.0 x10^9/L and the platelet count >100 x10^9/L. Blood counts should be done at least once every 28 days (ie with each VCR) or more frequently if dose adjustment of 6MP is necessary (see 11.3). Liver function tests (LFT's) are recommended every 8 weeks or more frequently if clinically indicated. **Continue** trimethoprim-sulfamethoxazole prophylaxis.

11.1 Vincristine 1.5mg/m^2 IV (maximum dose 2mg) every 28 days (see 7.41).

11.11 Vincristine and the 5 day pulse of dexamethasone are to be given together every 28 days irrespective of blood count (see 11.21).

11.2 Dexamethasone 6mg/m^2/day orally in 2 divided doses for 5 days every 28 days

11.21 Dexamethasone and the IV push of vincristine are to be given together every 28 days irrespective of blood counts (see 11.11).

11.3 6-mercaptopurine 75mg/m^2/day continuously

11.31 6MP is given once daily at bed time and without milk products. If vomiting occurs within 2 hours the full dose should be repeated. The aim is to give 350 mg/m^2/week as shown in the table on page 17.

11.**32** An FBC is performed every 28 days prior to each vincristine and dexamethasone pulse. If the neutrophil count drops to between 0.5-1.0x10^9/L and/or the platelet count to 50-100 x10^9/L then both 6-mercaptopurine and methotrexate should be reduced by 25%. The count should then be repeated at weekly intervals.

11.33 When counts recover to neutrophils >1.0x10^9/L and platelets >100x10^9/L then resume therapy at standard dose.

11.34 If the neutrophil count is <0.5x10^9/L and/or the platelet count <50x10^9/L then oral 6-mercaptopurine and methotrexate are ceased. Upon recovery to neutrophils >1.0 and platelets >100 therapy is resumed at 50% of standard doses and increased to 75% and 100% as tolerated. (This will usually be at 2 week intervals).

11.35 For patients who maintain counts of neutrophils >2.0 x10^9/L **and** platelets >150 x10^9/L for a minimum of 2 weeks the dose of 6-mercaptopurine should be increased to 100 mg/m^2/day. If this dose is tolerated and compliance is verified, then the dose should be increased to 125 mg/m^2. The methotrexate dose remains constant at 20 mg/m^2/week.

11.36 If prolonged cytopaenia >3weeks, recommend stopping weekend cotrimoxazole. If still cytopaenic at 4-6 weeks recommend BMA to exclude relapse. Unhelpful often to do an earlier marrow as hypocellular marrows are difficult to interpret, so best to wait.

11.4 Methotrexate 20 mg/m^2 orally weekly

Oral methotrexate is given in the evening together with 6-mercaptopurine (see 9.31) –refer table on page 18.

11.41 Grade 2-4 nephrotoxicity (creatinine >2.6x upper limit of normal) - omit until toxicity resolved (Grade 0, creatinine <1.25x upper limit of normal).

11.42 Grade 3-4 hepatotoxicity - omit until Grade 0-2 toxicity then resume at half dose. Escalate dose at 2 weekly intervals, provided Grade 3-4 toxicity does not recur.

11.43 Grade 2 stomatitis (erythema, ulcer, can eat solids) of >3 days duration, decrease dose by 30%. Grade 3-4 stomatitis - withhold until resolved and resume dose at 50%.

11.44 The dose of oral methotrexate due on the week of intrathecal methotrexate is withheld.

11.45 Dose guidelines for methotrexate:
An FBC is performed every 28 days prior to each vincristine and dexamethasone pulse. If the neutrophil count drops to between 0.5-1.0x10^9/L and/or the platelet count to 50-100 x10^9/L then both 6-mercaptopurine and methotrexate should

be reduced by 25%. The count should then be repeated at weekly intervals.

11.46 When counts recover to neutrophils >1.0x10^9/L and platelets >100x10^9/L then resume therapy at standard dose.

11.47 If the neutrophil count is <0.5x10^9/L and/or the platelet count <50x10^9/L then oral 6-mercaptopurine and methotrexate are ceased. Upon recovery to neutrophils >1.0 and platelets >100 therapy is resumed at 50% of standard doses and increased to 75% and 100% as tolerated. (This will usually be at 2 week intervals).

11.48 There is no dose escalation above 20mg/m^2/day during this phase irrespective of counts

11.5 Intrathecal methotrexate .

All patients receive intrathecal methotrexate in age related doses

Age	1-2 years	2-3 years	> 3 years
Dose	8 mg	10mg	12mg

Send CSF for cytospin.

11.51 Intrathecal methotrexate is given every 8 weeks during continuation therapy until completion of 12 months of treatment from time of remission (see 9.54).

11.52 The dose of oral methotrexate at this time is withheld (see 11.44).

11.53 Intrathecal methotrexate is given every 8 weeks but should be deferred if the absolute neutrophil count is <0.5 x10^9/L and/or platelet count is <50 x10^9/L.

11.54 IT MTX is ceased after the first year of therapy

11.6 Continuation therapy is given until 2 years of treatment from the time of documentation of remission has been given (see 7.0, 9.0).

11.7 Record details of therapy (when IV vincristine and IT methotrexate/oral 6MP and MTX given) on the flow sheets (to be circulated). This will facilitate protocol review and audit for producing outcome data.

11.8 Non- compliance. If families non-compliant and cease therapy, and the child subsequently relapses, symptomatic treatment will be required. (see 10.5).

12.0 COMPLETION OF THERAPY

Following completion of 2 years of therapy from documentation of remission (see 7.33), a bone marrow aspirate and diagnostic lumbar puncture will be performed. If continuing complete remission is documented therapy is ceased and the patient moves into follow-up. If remission is not documented, then symptomatic treatment will be required.

12.1 Patients will need to be followed at set intervals to document progress including continuing remission and late effects of treatment (if any- expected to be minimal). A full blood count should be performed at

the first visit off treatment and if normal no further blood tests unless clinically indicated.

12.2 When off treatment 6 months, provided well and in remission, re-immunise as per recommended schedule- refer chapter on infections.

12.3 Relapse

12.31 Bone marrow relapse - >25% lymphoblasts irrespective of the proportion of lymphocytes. If marrow rating is M_2 (5-25% lymphoblasts) the marrow should be repeated in 4 weeks time.

12.32 CNS relapse - >5 white cells $x10^6$/L plus cytocentrifuge examination confirming morphologically unequivocal lymphoblasts.

12.33 Testicular relapse - unilateral or bilateral testicular enlargement. Biopsy is required to confirm diagnosis.

12.34 All patients should have both bone marrow examination and CSF examination performed at the time of relapse.

12.4 Death.

12.5 Parents' or patient's refusal to follow assigned therapeutic regimen. Follow up data will still be required for these patients.

MERCAPTOPURINE 60 mg/m^2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.33 - 0.38	½ tab / d x 6	150 mg/wk
0.39 - 0.44	½ tab / d x 7	175 mg/wk
0.45 - 0.50	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.51 - 0.56	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.57 - 0.62	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.63 - 0.68	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.69 - 0.74	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.75 - 0.80	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.81 - 0.86	1 tab / d x 7	350 mg/wk
0.87 - 0.92	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.93 - 0.98	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.99 - 1.04	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
1.05 - 1.10	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.11 - 1.16	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.17 - 1.22	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.23 - 1.27	1½ tab / d x 7	525 mg/wk
1.28 - 1.33	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.34 - 1.39	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.40 - 1.45	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.46 - 1.51	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.52 - 1.57	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.58 - 1.63	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.64 - 1.69	2 tab / d x 7	700 mg/wk
1.70 - 1.75	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.76 - 1.81	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.82 - 1.87	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.88 - 1.93	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.94 - 1.99	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
2.00 - 2.05	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
2.06 - 2.11	2½ tab/ d x 7	875 mg/wk
2.12 - 2.17	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
2.18 - 2.23	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
2.24 - 2.29	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
2.30 - 2.35	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
2.36 - 2.41	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
2.42 - 2.47	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
2.48 - 2.52	3 tab/ d x 7	1050 mg/wk
2.53 - 2.58	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.59 - 2.64	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.65 - 2.70	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.71 - 2.76	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.77 - 2.82	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.83 - 2.88	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk

MERCAPTOPURINE 75 mg/m^2

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk

METHOTREXATE 20mg/m^2/week			
surface area	Dose per week (mg)	number of tablets	
		2.5mg	10mg
0.4	7.5	3	-
0.41 – 0.46	8.75	3 ½	-
0.47 – 0.53	10	-	1
0.54 – 0.59	11.25	½	1
0.6 – 0.65	12.5	1	1
0.66 – 0.71	13.75	1 ½	1
0.72 – 0.78	15	2	1
0.79 – 0.84	16.25	2 ½	1
0.85 – 0.9	17.5	3	1
0.91 – 0.96	18.75	3 ½	1
0.97 – 1.03	20	-	2
1.04 – 1.09	21.25	½	2
1.1 – 1.15	22.5	1	2
1.16 – 1.21	23.75	1 ½	2
1.22 – 1.28	25	2	2
1.29 – 1.34	26.25	2 ½	2
1.35 – 1.4	27.5	3	2
1.41 – 1.46	28.75	3 ½	2
1.47 – 1.53	30	-	3
1.54 – 1.59	31.25	½	3
1.6 – 1.65	32.5	1	3
1.66 – 1.71	33.75	1 ½	3
1.72 – 1.78	35	2	3
1.79 – 1.84	36.25	2 ½	3
1.85 – 1.9	37.5	3	3
1.91 – 1.96	38.75	3 ½	3
1.97 – 2.03	40	-	4
2.04 – 2.09	41.25	½	4
2.1	42.5	1	4

13.0 SAMPLE PARENT INFORMATION SHEET

Parent Information Sheet

Pacific Acute Lymphoblastic leukaemia Protocol

Your child has acute lymphoblastic leukaemia (ALL). This is a disorder of unknown cause where there is unrestrained growth of abnormal lymphoblasts (primitive white blood cells) in the bone marrow. Because the production of these abnormal cells is uncontrolled the bone marrow is unable to produce usual numbers of normal red blood cells, white blood cells and platelets. Once produced in the bone marrow, the leukaemic cells (lymphoblasts) have the potential to spread to any part of the body.

ALL is now a curable disease in some children. Research has lead to the identification of certain features of ALL which are present at diagnosis. Such features are referred to as prognostic features. Depending on the prognostic features present at diagnosis, children with ALL can be divided into subgroups, with some groups having a good chance of cure, and some groups having a poor chance of cure. Children who have a good chance for cure will be offered treatment on this protocol. It is impossible to predict whether an individual child will be cured. This information has been designed to help you understand the principles of treatment of ALL and the way it will be given to your child. Remember there are differences between the features present at diagnosis in children with ALL. It is important to remember this fact when discussing and comparing your child's diagnosis, treatment, and progress with other families.

Your consultant will keep you fully informed. Should you have any questions regarding your child's illness or treatment please ask the staff caring for your child. As leukaemia is an illness which has an impact on the whole family, it is important everybody understands how the treatment is given, and why it is given in the way it is. The family is an equally important part of the treatment team as are the doctors, nurses, social workers, pharmacists, chaplains etc.

Your child will receive standard antileukaemic treatment according to this protocol

The therapy on this protocol is divided into a number of phases. It continues over two years provided the child remains leukaemia free. Your consultant will discuss all aspects of the treatment with you and provide you with a copy of the treatment your child is scheduled to receive. Initial treatment, called prednisone prephase will be given to all patients. A good response to this treatment will improve your child's chance of being cured. The next phase is remission induction. This phase, lasting four weeks is aimed at making the leukaemia disappear. This is achieved in most patients. The ongoing treatment is aimed at preventing return of the leukaemia (relapse). More than 60% of patients should remain free of leukaemia at the end of treatment. The next phase of treatment, called CNS preventative/consolidation therapy lasts four weeks. CNS preventative therapy provides treatment directly to the central nervous system (CNS) by injecting drugs directly into the spinal fluid by means of a lumbar

puncture. This is referred to as intrathecal therapy. Consolidation therapy is also given at this time.
Interim Maintenance therapy allows time for the child to recover before a delayed intensification phase is given. This treatment is the same treatment which will be given for most of the next 2 years of therapy. This phase lasts 8 weeks.
Delayed Intensification which lasts 8 weeks is a repeat of the first 2 phases of treatment. International experience has shown that repeating this type of intensive therapy significantly improves outcome for children with ALL. It does however require frequent treatment and a need to remain close to the treatment centre.

Continuation therapy follows. This phase lasts until the end of treatment. It consists of oral and intravenous therapy. Intrathecal therapy is given every eight weeks during continuation therapy until one year of treatment is completed.

The following is a list of drugs your child may be given. The treatment may need to be modified according to your child's tolerance and side effects he/she experiences. If you have questions please ask a staff member. The most common side effects are listed below:-

Vincristine (VCR) – Given intravenously
- Skin burn if the drug leaks from the vein
- Constipation
- Jaw pain
- Convulsions
- Hair loss
- Leg pain
- Low blood counts

Prednisone (PDN) – given orally
- Weight gain
- Water retention
- Irritability
- High blood pressure
- Diabetes
- Decreased ability to fight infection

Dexamethasone (DEX) – given orally
- As for prednisone

L-Asparaginase (L-Asp) – given by injection into the muscle
- Allergic reactions
- High blood sugar
- Inflammation of the pancreas
- Liver function abnormalities
- Loss of appetite and lethargy

Methotrexate (MTX) – given intrathecally
- Irritation of the membranes around the brain and spine
- Convulsions
- Headache, backache, fever
- Learning difficulties

Methotrexate (MTX) – given orally or intravenously

- Nausea and vomiting
- Mouth ulcers
- Rash
- Liver or kidney function abnormalities
- Learning difficulties
- Low blood counts

Cytarabine (Ara-C) – given by injection under the skin or intravenously

- Nausea and vomiting
- Low blood counts
- Rash and fever

Cytarabine (Ara-C) – given intrathecally

- As for Methotrexate given intrathecally
- (only used if intrathecal methotrexate unable to be given)

Doxorubicin – given intravenously

- Nausea and vomiting
- Skin burn if the drug leaks from the vein
- Hair Loss
- Effects on heart function (rare at these low doses)

Cyclophosphamide – given intravenously

- Nausea and vomiting
- Hair loss
- Low blood counts
- Bladder irritation
- Infertility (very rare)
- Second cancers (very rare)

6-Mercaptopurine (6MP) – given orally

- Low blood counts
- Liver function abnormalities
- Anorexia

Your consultant will discuss in detail all phases of the treatment protocol your child will receive, including the side effects and possible complications associated with treatment. You need to be informed of the range of possible side effects. Some children will experience few of the side effects while other children may experience many. Whilst your child will follow the protocol, the exact treatment received will be adjusted to allow for individual tolerance. Again this may seem to mean differences in treatment of the same disease during discussion with other families.

We hope this information is helpful to you and will enable you, your child and family to understand and cope with the necessary treatment which we hope will achieve cure.

14.0 TREATMENT SCHEMA

PI ALL- 2 protocol

Prephase/Induction							**5 weeks**
Days	**-7**	**1**	**8**	**15**	**22**	**29**	**36/1**
	M_{it}			M_{it}		M_{it}	
	V	V	V	V			
				L L L	L L L	L L L	
	PPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPP						
	BMA					BMA	

Key	**Drug**	**Dose**	**Route**	**Days**
M_{it}	Methotrexate	Age related (max 12mg)	IT	-7, 15, 29
V	Vincristine	1.5 mg/m^2 (max 2mg)	IV	1,8,15,22
L	*E. Coli* L-asp.	6000 U/m^2 x9 doses	IM	Mon-Wed-Fri
P	Prednisone	40mg/m^2/day	O	-7 to 22

BMA Bone marrow aspirate on days -7, 29

CNS Preventative/Consolidation Therapy						**6 weeks**
Days	**1**	**8**	**15**	**22**	**29/1**	
	M_{it}	M_{it}	M_{it}			
	C			C		
	AAAA	**AAAA**		**AAAA**	**AAAA**	
	6666666666666666666666666666666					

Key	**Drug**	**Dose**	**Route**	**Days**
M_{it}	Methotrexate	Age related (max 12mg)	IT	1,8,15
6	6 Mercaptopurine	60 mg/m^2	O	1 to 28
C	Cyclophosphamide	1000 mg/m^2	IV infuse x1hr	1/22
A	Ara-C	75 mg/m^2/day	SC	1-4,8-11,and 22-25, 29-32

Pneumocystis prophylaxis See Appendix A1.1

Interim Maintenance Therapy									**8 weeks**
Days	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57/1**
					M_{it}				
	V				V				
	DDDDD				**DDDDD**				
	66666666666666666666666666666666666666666666666								
	M	M	M	M		M	M	M	

Key	**Drug**	**Dose**	**Route**	**Days**
M_{it}	Methotrexate	Age related (max 12mg)	IT	29
V	Vincristine	1.5 mg/m^2 (max 2mg)	IV	1,29
D	Dexamethasone	6 mg/m^2/day	O	1-5, 29-33
6	6-mercaptopurine	75 mg/m^2/day	O	1-56
M	Methotrexate	20 mg/m^2/week	O	1,8,15,22,36,43,50 (omit Day 29 as IT given)

Delayed Intensification Therapy — 8 weeks

Days	1	8	15	22	29	36	43	50	57/1
	M_{it}				M_{it}	M_{it}			
	V	V	V						
	L	L	L	L	L	L			
	Doxo	Doxo	Doxo						
	DDDDDDD		DDDDDDD						
					66666666666				
					C				
					AAAA	AAAA			

Key	Drug	Dose	Route	Days
V	Vincristine	1.5 mg/m^2 (max 2mg)	IV	1,8,15
Doxo	Doxorubicin	25 mg/m^2	IV	1,8,15
L	*E. Coli* L-asp.	6000 U/m^2 x 6 doses	IM	Mon,Wed,Fri from day 3
D	Dexamethasone	10mg/m^2/day	O	1-7, 15-21
M_{it}	Methotrexate	Age related (max 12mg)	IT	1,29,36
6	6 Mercaptopurine	60 mg/m^2	O	29-43
C	Cyclophosphamide	1000 mg/m^2	IV infuse x1hr	29
A	Ara-C	75 mg/m^2/day	SC	29-32, 36-39

Continuation Therapy — 84 weeks

Days	1	8	15	22	29	36	43	50	57/1
	M_{it}								M_{it}
	V				V				V
	DDDDD				**DDDDD**				**DDDDDD**
	66666666666666666666666666666666666666666666666666								
	M*	M	M	M	M	M	M	M	M*

Key	Drug	Dose	Route	Days
M_{it}	Methotrexate	Age related (max 12mg)	IT	1 ***First year only***
V	Vincristine	1.5 mg/m^2 (max 2mg)	IV	1,29
D	Dexamethasone	6 mg/m^2/day	O	1-5, 29-33
6	6-mercaptopurine	75 mg/m^2/day	O	1-56
M	Methotrexate	20 mg/m^2/week	O	1,8,15 etc (*omit if IT given)

APPENDIX 1

A1.1 *Pneumocystis* prophylaxis

All patients should receive prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ). This should commence with the consolidation phase of chemotherapy (section 8). TMP-SMZ then continues throughout therapy.
The dose is 5 mg/kg/day of TMP given in 2 divided doses for 2 days/week

Cotrimoxazole Liquid (240mg/mL) Dose - Twice Daily on Saturday and Sunday			
Weight of Patient (kg)	**Suspension 240mg/5ml**	**Dose of combined cotrimoxazole (mg)**	**Dose of trimethoprim component (mg)**
3 to 3.9	**1mL**	48	8
4 to 5.5	**1.5mL**	72	12
5.6 to 7	**2mL**	96	16
7.1 to 8.8	**2.5mL**	120	20
8.9 to 10.4	**3mL**	144	24
10.5 to 12	**3.5mL**	168	28
12.1 to 13.6	**4mL**	192	32
13.7 to 15.2	**4.5mL**	216	36
15.3 to 16.8	**5mL**	240	40
16.9 to 18.4	**5.5mL**	264	44
18.5 to 20	**6mL**	288	48
20.1 to 21.6	**6.5mL**	312	52
21.7 to 23.2	**7mL**	336	56
23.3 to 24.8	**7.5mL**	360	60
24.9 to 26.4	**8mL**	384	64
26.5 to 28	**8.5mL**	408	68
28.1 to 29.6	**9mL**	432	72
29.7 to 31.2	**9.5mL**	456	76
31.3 to 32.8	**10mL**	480	80
Cotrimoxazole tablet (480mg) Dose - Twice Daily on Saturday and Sunday			
Weight of Patient (kg)	**480mg tablet**	**Dose of combined cotrimoxazole (mg)**	**Dose of trimethoprim component (mg)**
15 to 22.5	**½ tablet**	240	40
22.6 to 37.5	**1 tablet**	480	80

Cotrimoxazole Liquid (240mg/mL) Dose - Twice Daily on Saturday and Sunday			
37.6 to 52.5	**1 ½ tablets**	720	120
> 52.6	**2 tablets**	960	160

A1.2 Cyclophosphamide in consolidation and delayed intensification (section 8.21, 10.5)

i) Prehydrate with dextrose/saline (0.18% saline + 4% dextrose or 0.3% saline and 3.5% dextrose) + 20mmol/L potassium chloride at 125mL/m^2/hr for 2 hours.

ii) $5HT_3$ antagonist (ondansetron) if available, otherwise metoclopramide for nausea and vomiting.

iii) Give cyclophosphamide 1000mg/m^2 in 125mL/m^2 0.9% N saline over 1 hour OR **add cyclophosphamide 1000 mg/m^2 to 50 mL of N saline or 5% dextrose and infuse over 1 hour as a side line together with hydration fluid at 125mL/m^2/hour (preferred)**.

iv) When cyclophosphamide is completed continue hydration fluid rate at 125mL/m^2/hour for 4 hours post cyclophosphamide.

A1.3 Parental handling of oral medication (6MP/MTX)

i. Wash hands before and after handling tablets.
ii. For halving tablets either use a pill cutter or a clean knife-dedicated for this use only.
iii. Gloves are not necessary.
iv. Store tablets at room temperature.