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Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 15: CENTRAL NERVOUS SYSTEM CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2016 -2018)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the central nervous system chapter

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
15.1 Stroke – acute management	Amlodipine, oral	Not added as a pre-referral dose
	Aspirin	Added as a pre-referral dose
15.2 Dementia	n/a	n/a
15.3.2 Epilepsy	Monotherapy	Retained
	Combination therapy	Not added
	Therapeutic drug monitoring of anti-epileptic medicines	Amended
- Children	Phenobarbital, oral	Retained as management for general tonic seizures in children
	Carbamazepine, oral	Dosing amended and doctor prescribed
	Valproic acid	Not added
- Adults	Lamotrigine, oral	Dosing amended; note pertaining to preference for use in pregnancy added and adverse drug reaction of SJS/TEN not added
	Valproic acid	Caution in women of childbearing potential added
15.4.1 Meningitis, acute	Corticosteroids	Not added
- Listeria outbreak	Ampicillin IM/IV	Added
	Cotrimoxazole, oral	Added as pre-referral dose in penicillin allergic patients
15.5.2 Bells palsy	Prednisone, oral	Directions for initiation of treatment amended
	Lanolin anhydrous eye ointment	Not added

15.1 STROKE

Acute management

Amlodipine, oral: *not added as a pre-referral dose*

The PHC Committee proposed that a single pre-referral dose of amlodipine be recommended for conscious stroke patients with BP > 220/120 mmHg, aligned with Adult Hospital Level STGs and EML, 2015.

Acute pre-referral treatment for adults

Note: Only for patients who are conscious and able to swallow without difficulty:

If BP > 220/120mmHg:

- Long-acting calcium channel blocker e.g.:
- Amlodipine, oral, 5 mg as a single dose (after consultation with a doctor or specialist).

Annotate referral letter to include date and time of administration of single dose of amlodipine 5mg and any other medication

Level of Evidence: I Systematic review[1], RCT[2], Guidelines[3]

NEMLC DISCUSSION AT THE MEETING OF 29 JUNE 2017:

Amlodipine, oral, as a pre-referral dose: The lack of evidence of administering amlodipine, oral as a pre-referral dose for patients with BP > 220/120 mm HG in the PHC setting was discussed. However,

[1] Citation in Adult Hospital Level STGs and EML, 2015: Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014 Oct 28;10:CD000039. http://www.ncbi.nlm.nih.gov/pubmed/25353321

[2] Citation in Adult Hospital Level STGs and EML, 2015: He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, Tong W, Liu C, Xu T, Ju Z, Peng Y, Peng H, Li Q, Geng D, Zhang J, Li D, Zhang F, Guo L, Sun Y, Wang X, Cui Y, Li Y, Ma D, Yang G, Gao Y, Yuan X, Bazzano LA, Chen J; CATIS Investigators. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014 Feb 5;311(5):479-89.

[3] Adult Hospital Level STGs and EML, 2015.

the NEMLC was of the opinion that there are potential harms associated with this recommendation. **Recommendation**: Single pre-referral dose of amlodipine 10 mg for conscious stroke patients with BP > 220/120 mmHg, not be added to the STG.

Aspirin, oral: *added as pre-referral dose*

Refer to medicine review for detailed information:

Aspirin_Pre-referral Dose_ AcuteStroke_

Based on this evidence review, the Primary Health Care Committee recommends a pre-referral dose of aspirin 300 mg for acute presumptive stroke, presenting at primary level of care.

Rationale: Evidence of a moderate benefit of aspirin outweighing harms of aspirin as a pre-referral dose in reducing recurrent ischaemic stroke of unknown aetiology.

Level of Evidence: I Meta-analyses[4] [5]

NEMLC DISCUSSION AT THE MEETING OF 12 APRIL 2018:

The NEMLC accepted the PHC Committee's recommendation on pre-referral dose of aspirin 300 mg for acute presumptive stroke, presenting at primary level of care. However, a number of caveats were discussed, and it was recommended that the following exceptions be included in the STG:

- Unconscious patients
- Symptoms suggestive of a sub-arachnoid bleed, e.g. headache, stiff neck, etc.
- Patients that can be transferred to a facility for thrombolysis within 3 hours.

NEMLC Recommendation: Pre-referral dose of aspirin be recommended for acute presumptive stroke at primary level of care, except in patients as listed above.

Referral

STG text amended as follows:

~~Refer urgently for consideration of thrombolysis if symptom duration is < 4.5 hours.~~
~~All patients including patients with TIA.~~
Refer all acute stroke cases for further management (preferably within 3 hours).

Rationale: Continuum of care considered - Adult Hospital Level STG to recommend fibrinolytics (alteplase, tenectaplase) for acute stroke, as approved on the Tertiary & Quaternary EML that indicates administration within 3 hours.

Level of Evidence: III Guidelines

15.2 DEMENTIA

NEW SECTIONS(S)/ SUBSECTION(S)

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
15.2	**Dementia**	No	n/a

On receipt of an external stakeholder comment for guidance on dementia at primary level of care, the following new STG was recommended for inclusion to the chapter, adapted from the Adult Hospital level STGs and EML, 2015 (section 14.2: Dementia).

15.2 Dementia

Description

[4] Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014(3):CD000029.

[5] Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet (London, England). 2016;388(10042):365-75.

Progressive loss of cognitive function, usually of insidious onset. Initial presentation may be with mild personality or memory changes, before more pronounced defects become evident.
Common reversible causes of dementia include:

» Metabolic
- Hypothyroidism
- Vitamin B12 deficiency
- Pellagra
- Thiamine deficiency (Wernickes syndrome)

» Medications and drugs
- Alcohol abuse
- Many medications with CNS side effects

» » Infections
- Syphilis
- HIV dementia

» Surgical
- Chronic subdural haematoma
- Normal pressure hydrocephalus

» Severe depression

Conditions which may worsen already existing dementia include:

» Electrolyte disturbances and dehydration.
» Infections, usually originating from the respiratory or urinary tract.
» Medication toxicity.

Referral
All patients.

Level of Evidence: III Guidelines

15.3.2 EPILEPSY

Monotherapy: *retained*
Combination therapy: *not added*
Therapeutic drug monitoring of anti-epileptic medicines: *amended*

External comments were received for the following:

- Combination therapy to be considered at primary level of care. However, the PHC STG advises monotherapy and management with combination therapy is done at higher levels of care.
  Level of Evidence: III Expert opinion

- Therapeutic drug monitoring should not be done routinely, except to confirm non-adherence or monitor for toxicity.
  The text of the STG was updated as follows:

  – In patients receiving any ~~other~~ anticonvulsants, therapeutic drug monitoring may be useful to confirm suspected non-adherence, or diagnose toxicity in a symptomatic patient.
  – Therapeutic drug monitoring should be done in patients receiving higher than usual doses of phenytoin to confirm non-adherence or clinical evidence of toxicity.

  Level of Evidence: III Expert opinion[6]

  NEMLC DISCUSSION AT THE MEETING OF 12 APRIL 2018:
  The NEMLC recommended that the editorial amendment in the STG be strengthened, emphasising that Therapeutic Drug Monitoring should not be done routinely in patients on anti-epileptic drugs, except to confirm non-adherence or monitor for toxicity. Text of STG was further editorially amended as follows:

[6] Stepanova D, Beran RG. The benefits of antiepileptic drug (AED) blood level monitoring to complement clinical management of people with epilepsy. Epilepsy Behav. 2015 Jan;42:7-9. https://www.ncbi.nlm.nih.gov/pubmed/25499154

- In patients receiving any anticonvulsants, therapeutic drug monitoring may be useful to confirm suspected non-adherence, or diagnose toxicity in a symptomatic patient.
- Therapeutic drug monitoring should be done in patients receiving higher than usual doses of phenytoin to confirm non-adherence or clinical evidence of toxicity.

Generalised tonic clonic seizures

Children

Phenobarbitone, oral: *retained as management for general tonic seizures in children*

External comment was received that *"There is a background of concern in the literature regarding the safety and neurobehavioural adverse effect profile of phenobarbital in young children".*

In the previous PHC review cycle, evidence was reviewed: RCT[7] (n=108 children, aged 2-15 with generalised tonic-clonic (n=51) or partial & secondary generalised seizures (n=57)) showed no excess in behavioural side effects with phenobarbital in children with epilepsy in a country with limited resources (Bangladesh).

Recommendation: Phenobarbitone, oral be retained in the STG for management for general tonic seizures in children.

Rationale: There is a paucity of data to suggest that phenobarbitone affects cognitive development. There is no further evidence to that which was previously reviewed.

Level of Evidence: I RCT

Carbamazepine, oral: *paediatric dosage amended*

Aligned with guidelines.

Level of Evidence: III Guidelines[8] [9]

Valproic acid, oral: *not added*

During the previous PHC 2012-2014 review cycle, valproic acid was considered too expensive for inclusion in the primary level EML[10]. The PHC Committee was of the opinion that valproic acid was still unaffordable.

Medicine	Price in 2014[11]	Price in 2017[12]
Sodium Valproate 100mg 100 Tablet, crushable	R 75.00	R 78.75
Valproate Sodium and Valproic Acid 133.2/58mg 100 Tablet	R 39.08	R 42.01
Valproate Sodium and Valproic Acid 133.2/58mg 56 Tablet	R 24.07	R 26.62
Valproate Sodium and Valproic Acid 199.8/87mg 100 Tablet	R 57.65	R 61.98
Valproate Sodium and Valproic Acid 199.8/87mg 56 Tablet	R 35.51	R 38.24
Valproate Sodium and Valproic Acid 333/145mg 100	R 90.87	R 97.61
Valproate Sodium and Valproic Acid 333/145mg 56 Tablet	R 55.97	R 60.23
Valproate Sodium 200mg/5ml 300 mL	R 106.02	R 107.58

Level of Evidence: III Expert opinion

Below is the previous NEMLC report (27 March 2014 providing the rationale for not including valproic acid to the PHC EML:

Extract from the NEMLC report for PHC Level STGs and EML, 2015: Chapter 15Central nervous system conditions

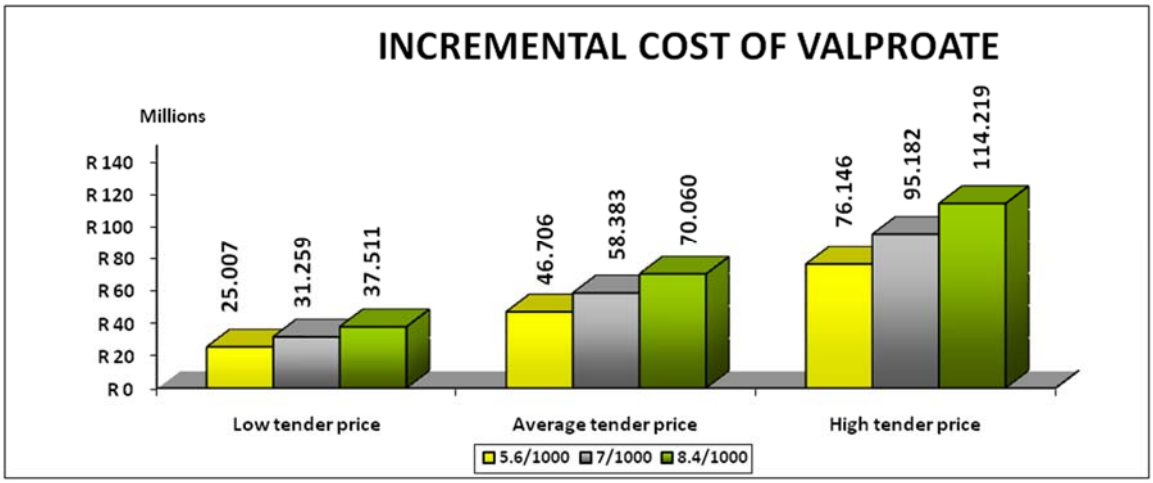
[7] Banu SH, Jahan M, Koli UK, Ferdousi S, Khan NZ, Neville B. Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. *BMJ*. 2007 Jun 9;334(7605):1207.
[8] Paediatric Hospital level STGs and EML, 2017
[9] BNF for children, 2011-2012.
[10] NEMLC minutes of the 27 March 2014.
[11] November 2014: Contract circulars HP09-2014SD; HP12-2014LQ
[12] June 2017: Contract circulars HP09-2016SD; HP12-2014LQ

Valproate: Evidence shared by the Paediatric Hospital level committee suggested that valproate was more efficacious than lamotrigine:
In the SANAD[13]unblinded randomised controlled trial, 716 patients from hospital-based outpatient clinics were randomly assigned to valproate, lamotrigine, or topiramate and follow-up data up to 1 year was obtained.

Results were as follows:

Effect	Hazard ratio	95% CI
Overall analysis		
Time to treatment failure- topiramate: valproate	1.57	1.19 to 2.08
Time to treatment failure- lamotrigine: valproate	1.25	0.94 to 1.68 (NS)
In the subgroup analysis: idiopathic generalised epilepsy		
Time to treatment failure – topiramate: valproate	1.89	1.32 to 2.70
Time to treatment failure – lamotrigine: valproate	1.55	1.07 to 2.24
Overall analysis		
Time to 12-month remission: valproate:lamotrigine	0.76	0.62 to 0.94
In the subgroup analysis: idiopathic generalised epilepsy		
Time to 12-month remission: valproate: lamotrigine	0.68	0.53 to 0.89

Cost: A cost model comparing the annual budget impact of valproate versus carbamazepine for generalised tonic-clonic seizures in children follows. The model was based on a prevalence study[14] in rural South African children that suggested a prevalence of 7.3/1000 in the 2-5 year age group and 6.7/1000 in the 6-9 year age group. Using the population statistics for 2011 from Stats SA, it was estimated that the epilepsy prevalence in <6 year age group was 43 531 and in the 6-12 year age group was 54 260. Costs were calculated for maintenance doses of AEDs, modelling on the average, high and low tender price for each intervention. In addition, sensitivity analyses were done for an epilepsy prevalence rate of 5.6/1000 and 8.4/1000. The incremental annual cost of therapy for valproate compared to carbamazepine is indicated below:



The PHC Committee raised concerns regarding the cost of valproate at PHC level. Currently, it was reported that ABC analyses in provinces features valproate amongst the top 5 medicines in approximately 70% of the provinces.

Recommendations:

- At primary care level where generalised tonic clonic seizures are treated that 1st line therapy for doctor initiated therapy of carbamazepine/ phenobarbitone should be recommended.
- If patients fail therapy initiated at PHC level, referral to secondary level for paediatrician care and consideration of valproate therapy should be recommended.

Rationale: Cost implications.

[13]Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ,Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, NicolaidesP,Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, WilliamsonPR; SANAD Study group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: anunblinded randomised controlled trial. Lancet. 2007 Mar 24;369(9566):1016-26.

[14] Christianson AL, Zwane ME, Manga P, Rosen E, Venter A, Kromberg JG. Epilepsy in rural South African children--prevalence, associated disability and management. S Afr Med J. 2000 Mar;90(3):262-6.

Adults

Lamotrigine, oral: *dosing amended; note pertaining to pregnancy added and adverse drug reaction of SJS/TEN not added*

- *Dosing:* Lamotrigine dosing updated, aligned with SAMF, 2016, as follows:

  - Lamotrigine, oral (Doctor initiated).
    - 25 mg daily for 2 weeks.
    - Then 50 mg daily for 2 weeks.
    - Thereafter, increase by 50 mg every 2 weeks according to response.
    - Usual maintenance dose: 100–200 mg daily as a single dose or divided doses.

- *Pregnancy:* Statement was added regarding lamotrigine being the preferred anti-epileptic agent in pregnancy aligned with Cochrane review[15]:

  Note: Lamotrigine is preferred in women of child-bearing potential.

  Level of Evidence: I Systematic review

Caution regarding valproic acid in pregnancy

The following caution was added to the STG, following the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) assessment and recommendation to strengthen the caution to avoid valproate exposure in pregnancy.

CAUTION

Children born to women taking valproic acid are at significant risk of birth defects (10%) and persistent developmental disorders (40%).
Valproic acid is contra-indicated and should be avoided in pregnancy and women of child-bearing potential.

Level of Evidence: III Registry data[16]

Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN): The PHC Committee was of the opinion that the STG was not a textbook, and the same caution is not added for other medicines. The skin chapter provides guidance for management of Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) - Section 5.10.6.1.

Medicine treatment

Medicine interactions:

Text of the STG was updated as follows, aligned with the Adult Hospital Level STGs and EML, 2015:

Medicine interactions

Phenytoin, phenobarbitone and carbamazepine are potent enzyme inducing agents and should be used with caution with other medicines metabolised by the liver, especially warfarin, ARVs, progestin subdermal implants and oral contraceptives.

» Progestin-only injectable contraceptivesor IUCDsare the preferred contraceptive methods forwomen of child-bearing potentialon anti-epilepticmedication. See Chapter 7: Family planning.

Level of Evidence: III Guidelines

HIV-infected individuals on ART

[15] Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11:CD010224. https://www.ncbi.nlm.nih.gov/pubmed/27819746

[16] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf

Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

Children

The following was aligned with the Paediatric Hospital level STGs and EML, 2016:

For HIV-infected children on ART, valproate is preferred because of fewer medicine interactions. When switching to valproate, commence treatment with maintenance dose of the medicine as below and discontinue the other anticonvulsant after 7 days. Exclude liver dysfunction prior to initiating therapy (at least ALT), in children < 2 years or if clinical suspicion of liver dysfunction.

Level of Evidence: III Guidelines

15.4.1 MENINGITIS, ACUTE

Corticosteroids: *not added*

External comment was received to align with NICE guideline to recommend urgent transfer without giving antibiotics, mainly to enable administration of dexamethasone within 4 hours of the first dose of antibiotics and because the disease progresses more slowly than septicaemia. However, this is not generalisable to the South African setting where urgent transfer to hospital is mostly not possible – NICE guidelines[17] then recommends that antibiotics be administered in primary care. Furthermore, corticosteroids have no clinical impact on mortality[18].

Listeria outbreak management

Ampicillin, IM/IV: *added as pre-referral dose*

Cotrimoxazole, oral: *added as pre-referral dose in penicillin allergic patients*

Aligned with NICD Guidelines, a pre-referral dose of ampicillin was added as concomitant treatment with ceftriaxone, IM, for management during a Listeria outbreak. However, in penicillin allergic patients, for practical purposes, a pre-referral dose of oral cotrimoxazole tablets was recommended rather than intravenous dose at primary level of care.

Level of Evidence: III Guidelines[19], Expert opinion

15.6.2 BELLS PALSY

Prednisone, oral: *initiation of treatment amended*

Cochrane review (2016) of 7 RCTs (n=895) showed that "overall, 79/452 (17%) participants allocated to corticosteroids had incomplete recovery of facial motor function six months or more after randomisation; significantly fewer than the 125/447 (28%) in the control group (RR 0.63, 95% CI 0.50 to 0.80; NNT 10 (95% CI 6 to 20). Corticosteroid treatment was within 72 hours of onset and only 1 RCT was studied children.

Double-blind, placebo-controlled RCT (2010) showed that patients (n=829) treated with prednisolone within 24 hours and 25 to 48 hours had significantly higher complete recovery rates, 66% (103/156) and 76% (128/168), than patients given no prednisolone, 51% (77/152) and 58% (102/177) (p = 0.008 and p = 0.0003, respectively) – intention to treat analysis. For patients treated within 49 to 72 hours of palsy onset, there were no significant differences. Funding was received by Pharma Industry.

The text of the STG was updated as follows:

- Prednisone, oral, 60 mg daily for 7 days started within 72 hours, preferably within 48 hours of onset (Doctor prescribed).

Level of Evidence: I Systematic review, RCT

Lanolin anhydrous eye ointment: *not added*

[17] NICE. Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. Clinical guideline 102; 2010. http://www.nice.org.uk/guidance/CG102

[18] Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015 Sep 12;(9):CD004405. https://www.ncbi.nlm.nih.gov/pubmed/26362566

[19] National Institute of Communicable Diseases. Listeriosis: Clinical recommendations for diagnosis and treatment, 5 December 2017. http://www.nicd.ac.za/

Evidence of efficacy: Recommended for patients with incomplete eye closure (short term complication) and have symptoms of eye irritation (burning, watering, decreased vision, sensitivity to light, eye pain). Clinical practice[20] [21] recommends prescribing of eye lubricants in Bells palsy with referral to an opthamologist if corneal abrasions are present.
Level of Evidence: III Standard of care

Usage creep and price: Restricting use only for patients with Bells palsy would be a challenge and usage creep would be a concern. Current contract price of a tube of lanolin anhydrous eye ointment (3.5 g) is R 35.90.[22]

*Epidemiology data:*There is a paucity of epidemiology data for South Africa. The annual incidence of Bell's palsy globally is approximately 15 to 40 cases per 100 000 people per year[23] with peak incidence usually between the ages of 15 and 50 years[24]. The majority of patients with facial nerve paralysis are expected to recover 85% within the first three weeks after the onset, while about 15% of recovery only starts after 2 to 3 months from onset[25].

Recommendation: Lanolin anhydrous eye ointment not be added to the EML at primary level of care in this clinical setting.
Rationale: The annual incidence of Bell's palsy globally is approximately 15 to 40 cases per 100 000 people per year and most patients with facial nerve paralysis are expected to recover 85% within the first three weeks after the onset, whilst about only 15% of recovery starts after 2 to 3 months from onset. The need for referral to an ophthalmologist if corneal abrasions are present would likely occur from secondary level of care.
Level of Evidence: III Global epidemiology data, Expert opinion
The following referral criterion was added to the STG:

Referral
» Non-responsive to treatment.
» All cases for physiotherapy.
» Eye irritation requiring lubrication.

[20]Gilden DH. Clinical practice. Bell's palsy. N Engl J Med 2004;351:1323-31.
[21] Holland NJ, Weiner GM. Recent developments in Bell's palsy. BMJ 2004;329:553-7.
[22] Contract circular HP07-2017DAI
[23]Hato N, Yamada H, Kohno H, Matsumoto S, Honda N, Gyo K, et al. Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebocontrolled study. OtolNeurotol2007;28:408-13.
[24]Zandian A, Osiro S, Hudson R, Ali IM, Matusz P, Tubbs SR, Loukas M. The neurologist's dilemma: a comprehensive clinical review of Bell's palsy, with emphasis on current management trends. Med SciMonit. 2014 Jan 20;20:83-90.
[25]Peitersen E. Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. ActaOtolaryngolSuppl 2002:4-30.