Opening and preparing a suspension of Alecensa

This article responds to your request for information on opening Alecensa® (alectinib) capsules and preparing a suspension from its contents.

In Brief

- Refer to your local label for recommended administration methods for Alecensa.
- Alecensa is formulated as an immediate-release, hard, size 1 capsule. There are currently no commercially available suspensions of alectinib chloride.
- Alecensa capsules should be taken with food and swallowed whole.
- A Phase 1 crossover, open-label, randomised study evaluated the relative bioavailability and pharmacokinetics (PK) of an Alecensa suspension versus capsule formulation in 28 healthy adult subjects:
    - The oral Alecensa suspension showed significantly higher peak and overall exposure than the Alecensa capsules, under fed and fasted conditions in healthy adults.
    - There were no apparent differences in incidence or severity of treatment-emergent adverse events between formulations.
- Clinical experience of preparing suspensions from Alecensa capsules for administration in the setting of non-small cell lung cancer (NSCLC) is limited to case reports in patients fitted with feeding tubes.

Abbreviations

AE= Adverse event

CT= Computerised tomography

NG= Nasogastric

NSCLC= Non Small Cell Lung Cancer

PEG= Percutaneous Endoscopic Gastrotomy

PET= Positron emission tomography

PK= Pharmacokinetics

Considerations

Alecensa capsules should be taken with food and swallowed whole. Do not open or dissolve the contents of the capsule.[1] Refer to the local label for Alecensa administration and handling information.

There are currently no commercially available solutions of alectinib hydrochloride. Data on efficacy has not been established with alternative dosage forms and routes of administration.

The decision whether to open Alecensa capsules lies with the physician and should be based on an appropriate assessment of the likely risk:benefit ratio. If Alecensa capsules were opened to make a suspension or sprinkle over food, we would advise appropriate clinical caution and monitoring.

Opening an Alecensa Capsule

Alecensa is formulated as an immediate-release, hard, size 1 capsule. The contents of an Alecensa capsule is white to yellow white powder, or powder with lumps.

Be aware that

- Alecensa is categorised as an anti-neoplastic agent,
- Alecensa has low solubility in aqueous buffers across the entire pH range,[2]
- opening capsules may scatter its ingredients, leading to inhalation and contact with active ingredients, and
- food compatibility studies have not been undertaken, therefore stability or drug release properties cannot be determined if the capsule contents are sprinkled on food.

Caution is advised if capsules are opened.

Bioavailability study

The relative bioavailability and pharmacokinetics of Alecensa administered as an oral suspension versus capsule was assessed in healthy adults under fasted and fed conditions.[3] This Phase I, crossover, open-label, randomised study was performed to infer suitability of Alecensa administered as a suspension to paediatric patients who cannot swallow capsules.

28 healthy adult volunteers received two single-dose Alecensa doses, two weeks apart. Volunteers were fed or fasted and were given doses of

- 4 x 150 mg Alecensa capsules (600mg total) and
- 600 mg Alecensa oral suspension.

The oral suspension was prepared by adding the contents of four 150 mg Alecensa capsules to 20 mL water to yield a drug concentration suspension of 30 mg/mL. This suspension was gently mixed (1:1) with apple juice and ingested within two hours of preparation.

The combined alectinib and M4 (active metabolite) exposure was higher for the suspension versus the capsules. The presence of food increased alectinib exposure regardless of formulation. Table 1 provides the relative bioavailability of alectinib and M4.

Table 1. Primary PK endpoints

PK parameter	Oral suspension vs capsule GMR (90% CI)
Fasted conditions	
AUC_{0-t} (h*nmol/L)	2.67 (2.28 - 3.10)
$AUC_{0-\infty}$ (h*nmol/L)	2.60 (2.23 - 3.04)

Cmax (nmol/L)	2.97 (2.61 - 3.37)
Mixed Fed	
AUC_{0-t} (h*nmol/L)	1.72 (1.40 - 2.11)
$AUC_{0-\infty}$ (h*nmol/L)	1.71 (1.40 - 2.06)
Cmax (nmol/L)	1.71 (1.39 - 2.11)
Abbreviations: $AUC_{0-\infty}$= area under the concentration–time curve extrapolated to infinity; AUC_{0-t}= area under the concentration–time curve from time 0 to the last measurable concentration; CI= confidence interval; Cmax= maximum observed concentration; GMR= geometric mean ratio; PK= pharmacokinetic.	

Single doses of 600mg alectinib oral suspension and capsules were well tolerated, with no serious AEs, AEs of special interest, or grade ≥3 AEs reported.

There were no observed differences in the incidence or severity of treatment-emergent AEs between formulations. Treatment-related AEs were reported in three subjects (10.7%) and included somnolence, abdominal pain, and headache; all were grade 1 in severity and were resolved at study completion.

Study summary

Alecensa suspension showed significantly higher peak and overall exposure than the Alecensa capsules under fed and fasted conditions in healthy adults. Poor solubility of alectinib is likely to have cause this effect. The publication authors stated that generating an oral suspension by vigorous stirring of capsule contents may have increased the soluble fraction, leading to increased drug absorption compared to intact capsules. The study concluded that an oral Alecensa suspension may be suitable for paediatric studies after appropriate dose adjustment.

The full publication provides more information on the PK and potential dose adjustment requirements.[3]

Case reports

Case reports of patients receiving an Alecensa suspension have been published. Table 2 describes these case reports in more detail. All patients in the case reports had stage IV ALK-NSCLC.

Table 2. Case reports of patients receiving Alecensa by suspension

Case	Patient details	Previous Treatment	Alecensa treatment	Outcome
Suspension adminsistered by feeding tube				

Watanabe et al. [4]	38 / M Unable to swallow due to mechanical ventilator dependence, and fitted with NG tube	1L: 1 course of platinum-based doublet chemotherapy 2L: 5 days of crizotinib, resulting in suspected crizotinib-induced pneumonitis Patient developed respiratory failure and underwent mechanical ventilation. Corticosteroids and a suspension of Alecensa were given.	Alecensa suspension (600 mg OD) administered via NG tube. The suspension was created by opening Alecensa capsules and dissolving contents in water. Patient received 11 days of Alecensa via NG tube, after which, the patient was weaned off ventilation and was able to swallow Alecensa capsules.	After 22 days of Alecensa, the patient was discharged from hospital. Chest X-rays and CT scans showed improved pneumonitis, and substantial tumour regression in both lungs. Patient remained on Alecensa without critical AEs.
Kanai et al. [5]	76 / F Unable to swallow due to dysphagia and somnolence, and was fitted with a NG tube	1L: Radiation therapy and crizotinib 2L: Pemetrexed	Alecensa suspension (300 mg BD) administered via NG tube. Patient received Alecensa suspension via NG tube for over 14 months.	Patient survived for over 14 months on Alecensa treatment, with no notable AEs.
Bejarano Vara et al.[6]	66 / F Unable to swallow due to dysphagia and was fitted with a NG tube and then PEG tube	1L: Crizotinib for 18 months, until stable disease was reported 2L: Palliative radiation	Alecensa suspension (600 mg BD) via NG / PEG tube. A 50 mg/mL suspension of Alecensa was prepared using an olive oil-based vehicle. Patient received 12 mL twice daily via NG/ PEG tube. Feeding tubes were flushed (30 mL) after each Alecensa administration. Patient was maintained on the Alecensa suspension for 30 days until able to swallow Alecensa capsules.	Patient achieved a near CR 12 weeks after the initiation of Alecensa suspension. Patient continued on Alecensa capsules without AEs.
Anderson et al.[7]	71/ F Fitted with a PEG tube	1L: 1 cycle of carboplatin, pemetrexed and pembrolizumab 2L: Alecensa capsules 600mg BD. 2 weeks after initiation patient developed a Grade 3 maculopapular rash Alecensa was withheld. Rash resolved within 1 week of steroid initiation. Patient subsequently underwent a desensitisation process to	A 5-step desensitisation process was initiated, target dose = Alecensa 300 mg BD. Contents of 2 x 150 mg capsules were dissolved in 40 mL of pharmaceutical grade olive oil to produce a 37.5 mg/5 mL suspension. Doses were self-administered by the patient via a PEG tube, followed by a 30 mL flush of tube feeding. Oral capsules resumed when the dose reached the	After 10-day desensitisation process the patient was able to tolerate Alecensa 300mg BD without recurrence of the rash or other significant AEs. At 3-week follow up, PET/CT revealed good response to therapy with no evidence of new or progressive disease. The patient remained on Alecensa 300 mg BD

		restart Alecensa, which required 5 days of low dose Alecensa.	standard capsule strength of 150 mg (day 5).	without concern.
Thomas et al [8]	90 / M Unable to swallow due to dysphagia and had a severely impaired general condition. Fitted with a PEG tube	Alecensa was the patient's first treatment for lung cancer	Alecensa suspension (600 mg BD) administered via PEG tube. Suspension created by opening Alecensa capsules and dissolving contents in water.	Alecensa was well tolerated, except for grade 2 hepatic cytolysis, which appeared after 10 days of treatment, and spontaneously decreased after 2 weeks. After 6 months of treatment patient's general condition improved and could swallow. After 10 months the patient continued to take Alecensa capsules orallly, and was in good physical form.
Suspension administered orally				
Ishiura et al [9]	56 / F Unable to swallow solid food or capsules, but could swallow liquids	1L: Surgery and radiotherapy	Contents of 2 x150 mg Alecensa capsules were dissolved in 100 mL water and administered via spoon over 30 minutes. Alecensa suspension (300 mg BD) administered for 3 months.	After 3 months, the patient had no swallowing difficulties and continued to receive Alecensa capsules. After 12 months of Alecensa the patient experienced a CR, without notable AEs.
Abbreivations: BD = Twice a day, CR=complete response, OD = Once a day, 1L = First line, 2L = Second line				

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