יוני 2019

Sprycel (dasatinib) 20, 50, 70 and 100 mg film coated tablets

ספרייסל (דסטיניב) 70,50,20 ו- 100 מ"ג טבליות מצופות

רופא/ה ,רוקח/ת יקר/ה,

ברצוננו להודיעך על עדכון בעלון לרופא ובעלון לצרכן של התכשיר ספרייסל (דסטיניב) בישראל.

ההתוויות התכשיר כפי שאושרו ע"י משה"ב:

Treatment of adult patients with:

* Newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.

* Chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate.

* Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

בפירוט שלהלן כלולים העדכונים המהותיים בלבד (טקסט שנוסף מסומן בצבע אדום ובקו תחתון,טקסט שהוסר מסומן בצבע אדום ~~ובקו אמצעי~~).

למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו על ידי משרד הבריאות.

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפס על ידי פנייה לבעל הרישום בריסטול- מאיירס סקוויב (ישראל) בע"מ.

בכבוד רב,

מיכל ניר ורדימון

מנהלת רגולציה

4. CLINICAL PARTICULARS

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4.4 Special warnings and precautions for use

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Important adverse reactions

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Thrombotic microangiopathy (TMA)

BCR-ABL tyrosine kinase inhibitors have been associated with thrombotic microangiopathy (TMA), including individual case reports for SPRYCEL (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving SPRYCEL, treatment with SPRYCEL should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with SPRYCEL should not be resumed.

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4.5 Interaction with other medicinal products and other forms of interaction

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Active substances that may decrease dasatinib plasma concentrations

When dasatinib was administered following 8 daily evening administrations of 600 mg rifampicin, a potent CYP3A4 inducer, the AUC of dasatinib was decreased by 82%. Other medicinal products that induce CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John´s Wort) may also increase metabolism and decrease dasatinib plasma concentrations. Therefore, concomitant use of potent CYP3A4 inducers with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative medicinal products with less enzyme induction potential should be used. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

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4.8 Undesirable effects

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Tabulated list of adverse reactions

The following adverse reactions, excluding laboratory abnormalities, were reported in patients in SPRYCEL clinical studies and post-marketing experience (Table 2). These reactions are presented by system organ class and by frequency. Frequencies are defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from available post-marketing data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Tabulated summary of adverse reactions

Infections and infestations	
Very common	infection (including bacterial, viral, fungal, non-specified)
Common	pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, (including cytomegalovirus - CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
Not known	hepatitis B reactivation

Blood and lymphatic system disorders	
Very Common	myelosuppression (including anaemia, neutropaenia, thrombocytopaenia)
Common	febrile neutropaenia
Uncommon	lymphadenopathy, lymphopaenia
Rare	aplasia pure red cell
Immune system disorders	
Uncommon	hypersensitivity (including erythema nodosum)
Endocrine disorders	
Uncommon	hypothyroidism
Rare	hyperthyroidism, thyroiditis
Metabolism and nutrition disorders	
Common	appetite disturbances[a], hyperuricaemia
Uncommon	tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
Rare	diabetes mellitus
Psychiatric disorders	
Common	depression, insomnia
Uncommon	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders	
Very common	headache
Common	neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
Uncommon	CNS bleeding*[b], syncope, tremor, amnesia, balance disorder
Rare	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders	
Common	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
Uncommon	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders	
Common	tinnitus
Uncommon	hearing loss, vertigo
Cardiac disorders	
Common	congestive heart failure/cardiac dysfunction*[c], pericardial effusion*, arrhythmia (including tachycardia), palpitations
Uncommon	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
Rare	cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
Not known	atrial fibrillation/atrial flutter
Vascular disorders	
Very common	haemorrhage*[d]
Common	hypertension, flushing
Uncommon	hypotension, thrombophlebitis, thrombosis
Rare	deep vein thrombosis, embolism, livedo reticularis
Not Known	thrombotic microangiopathy
Respiratory, thoracic and mediastinal disorders	
Very common	pleural effusion*, dyspnoea
Common	pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
Uncommon	pulmonary arterial hypertension, bronchospasm, asthma
Rare	pulmonary embolism, acute respiratory distress syndrome
Not known	interstitial lung disease
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain
Common	gastrointestinal bleeding*, colitis (including neutropaenic colitis), gastritis,

	mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
Uncommon	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
Rare	protein-losing gastroenteropathy, ileus, anal fistula
Not known	fatal gastrointestinal haemorrhage*
Hepatobiliary disorders	
Uncommon	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders	
Very common	skin rash[e]
Common	alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Uncommon	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder
Rare	leukocytoclastic vasculitis, skin fibrosis
Not known	Stevens-Johnson syndrome[f]
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[g]
Common	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
Uncommon	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis
Renal and urinary disorders	
Uncommon	renal impairment (including renal failure), urinary frequency, proteinuria
Not known	nephrotic syndrome
Pregnancy, puerperium and perinatal conditions	
Rare	abortion
Reproductive system and breast disorders	
Uncommon	gynecomastia, menstrual disorder
General disorders and administration site conditions	
Very common	peripheral oedema[gh], fatigue, pyrexia, face oedema[hi]
Common	asthenia, pain, chest pain, generalised oedema*[ij], chills
Uncommon	malaise, other superficial oedema[jk]
Rare	gait disturbance
Investigations	
Common	weight decreased, weight increased
Uncommon	blood creatine phosphokinase increased, gamma-glutamyltransferase increased
Injury, poisoning, and procedural complications	
Common	contusion

[a] Includes decreased appetite, early satiety, increased appetite.

[b] Includes central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.

[c] Includes brain natriuretic peptide increased, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure,cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesia.

[d] Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.

[e] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriaisis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.

[f] In the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to SPRYCEL or to concomitant medicinal product.

[g] Musculoskeletal pain reported during or after discontinuing treatment.

[h] Gravitational oedema, localised oedema, oedema peripheral.

[ih] Conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face.

[ji] Fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

[kj] Genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.

* For additional details, see section "Description of selected adverse reactions"

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5. PHARMACOLOGICAL PROPERTIES

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5.2 Pharmacokinetic properties

The pharmacokinetics of dasatinib were evaluated in 229 adult healthy subjects and in 84 patients.
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Distribution
In patients, dasatinib has a large apparent volume of distribution (2,505 L~~l~~), coefficient of variation (CV% 93%) suggesting that the medicinal product is extensively distributed in the extravascular space. At clinically relevant concentrations of dasatinib, binding to plasma proteins was approximately 96% on the basis of *in vitro* experiments.
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Elimination
The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 L/hr (CV% 81.3%).
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עדכונים מהותיים בעלון לצרכן:

2. לפני שימוש בתרופה:

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אזהרות מיוחדות הנוגעות לשימוש בתרופה:

יש ליידע את הרופא המטפל או הרוקח לפני הטיפול בספרייסל:

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- אם הופיעו חבורות , דימום, חום, תשישות ובלבול בזמן הטיפול בספרייסל, פנה לרופא. יתכן כי מדובר בסימנים של נזק לכלי דם, הידוע כמיקרואנגיופתיה תרומבוטית (thrombotic microangiopathy (TMA)).

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אם אתה נוטל, או אם נטלת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

מכיוון שהחומר הפעיל (דסטיניב) מסולק בעיקר על ידי הכבד, נטילת תרופות מסוימות יחד עם תרופה זו עלולה להשפיע על ריכוז תרופה זו בדם.

אין ליטול את התרופות הבאות יחד עם ספרייסל:

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- ~~דקסמתזון -קורטיקוסטרואיד~~

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4. תופעות לוואי:

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תופעות לוואי נוספות:

תופעות לוואי נפוצות מאוד (תופעות שמופיעות ביותר מ 1 מתוך 10 משתמשים):

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- **כאב:** כאב בשרירים (בזמן הטיפול או אחרי הפסקת הטיפול), כאבי בטן

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תופעות לוואי נוספות שדווחו עם תדירות לא ידועה (לא ניתן להעריך מהמידע הקיים) :

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- נזק לכלי דם הידוע כמיקרואנגיופתיה תרומבוטית ((thrombotic microangiopathy (TMA), כולל ירידה בספירת כדוריות דם אדומות , ירידה בטסיות והיווצרות של קרישי דם.