До реєстраційного посвідчення

№_____

від _____

Інструкція про застосування лікарського засобу або інформація про застосування лікарського засобу, затверджена згідно з нормативними вимогами країни Заявника/Виробника або країни, регуляторний орган якої керується високими стандартами якості, що відповідають стандартам, рекомендованим ВООЗ, та/або згідно з результатами клінічних випробувань, викладена мовою відповідно до вимог щодо мови, визначених абзацом другим частини третьої статті 26 Закону України «Про засади державної мовної політики»

БОГОЛЕПОВ А.А.

SANDOZ Nardo Alessia Aceto Sarah Jane stylegraph C.03210/7
Istruzione | Bosentan Sandoz compresse rivestite con film | 180 x 590 | VENDITA | ITALIA | 11/04/18
1 | NERO
1803-03 | A20013069/02 | 10428 | 8,5
IMPIANTI DI PROPRIETÀ DI SANDOZ S.p.A. VIETATO L'UTILIZZO NON AUTORIZZATO E LA MANOMISSIONE

APPROVED
By Oktay ÖZ at 8:07 pm, Apr 20, 2018

Foglio illustrativo: informazioni per l'utilizzatore

Bosentan Sandoz 62,5 mg compresse rivestite con film

Bosentan Sandoz 125 mg compresse rivestite con film

SANDOZ A Novartis Division

Medicinale equivalente

Legga attentamente questo foglio prima di prendere questo medicinale perché contiene importanti informazioni per lei.
- Conservi questo foglio. Potrebbe aver bisogno di leggerlo di nuovo.
- Se ha qualsiasi dubbio, si rivolga al medico o al farmacista.
- Questo medicinale è stato prescritto soltanto per lei. Non lo dia ad altre persone, anche se i sintomi della malattia sono uguali ai suoi, perché potrebbe essere pericoloso.
- Se si manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio, si rivolga al medico o al farmacista. Vedere paragrafo 4.

Contenuto di questo foglio:

1. Che cos'è Bosentan Sandoz e a cosa serve

Le compresse di Bosentan Sandoz contengono bosentan che blocca un ormone presente naturalmente nell'organismo chiamato endotelina-1 (ET-1), che causa un restringimento dei vasi sanguigni. Bosentan Sandoz comporta, quindi, una dilatazione dei vasi ed appartiene alla classe di medicinali denominati "antagonisti del recettore dell'endotelina".

Bosentan Sandoz è usato per trattare:
- **Ipertensione arteriosa polmonare** (PAH): la PAH è una malattia caratterizzata da un grave restringimento dei vasi sanguigni dei polmoni con conseguente aumento di pressione nei vasi sanguigni che portano il sangue dal cuore ai polmoni (arterie polmonari). Questa pressione riduce la quantità di ossigeno che può passare nel sangue attraverso i polmoni, rendendo l'attività fisica più difficoltosa. Bosentan Sandoz allarga le arterie polmonari, facilitando il pompaggio del sangue al loro interno da parte del cuore, ciò determina una riduzione della pressione sanguigna ed un'attenuazione dei sintomi.

  Bosentan Sandoz è usato per trattare pazienti affetti da ipertensione arteriosa polmonare (PAH) di classe III, per migliorare la capacità di esercizio (possibilità di svolgere attività fisica) ed i sintomi. La "classe" riflette la gravità della malattia: "classe III" comporta una marcata limitazione all'attività fisica. Alcuni miglioramenti sono stati evidenziati anche in pazienti con PAH di classe II. "Classe II" comporta delle minori limitazioni nell'attività fisica. La PAH per la quale Bosentan Sandoz è indicato può essere:
  - o primaria (senza una causa identificabile o familiare);
  - o causata dalla sclerodermia (definita anche sclerosi sistemica, una malattia caratterizzata da un'anormale crescita del tessuto connettivo che sostiene la cute ed altri organi);
  - o causata da difetti congeniti (innati) del cuore con shunt (vie di passaggio anormali) che determinano un flusso anormale di sangue attraverso il cuore ed i polmoni.
- **Ulcere digitali** (lesione delle dita di mani e piedi) in pazienti adulti con una condizione chiamata sclerodermia. Bosentan Sandoz riduce il numero delle nuove ulcere delle dita di mani e piedi.

2. Cosa deve sapere prima di prendere Bosentan Sandoz

Non prenda Bosentan Sandoz
- **se è allergico a bosentan** o ad uno qualsiasi degli altri componenti di questo medicinale (elencati al paragrafo 6)
- **se ha disturbi al fegato** (chieda al medico)
- **se è in gravidanza o può dare inizio ad una gravidanza** poiché non usa metodi anticoncezionali affidabili. Per favore legga le informazioni riportate in "Contraccettivi" e in "Altri medicinali e Bosentan Sandoz"
- **se è in trattamento con ciclosporina A** (un medicinale usato dopo un trapianto d'organo o per il trattamento della psoriasi)

Si rivolga al medico se una delle situazioni descritte sopra la riguarda.

Avvertenze e precauzioni

Si rivolga al medico o al farmacista prima di prendere Bosentan Sandoz.

Esami che saranno prescritti dal medico prima del trattamento
- un esame del sangue per verificare la sua funzionalità epatica
- un esame del sangue per controllare la presenza di anemia (emoglobina bassa)
- un test di gravidanza se lei è una donna in età fertile

In alcuni pazienti in terapia con Bosentan Sandoz sono stati riscontrati esiti anomali negli esami per la funzionalità epatica ed anemia (emoglobina bassa).

Esami che saranno prescritti dal medico durante il trattamento
Durante il trattamento con Bosentan Sandoz il medico le prescriverà regolarmente esami del sangue, in modo tale da monitorare eventuali cambiamenti della funzione del fegato e dei livelli di emoglobina.

Per tutti questi esami fare riferimento anche alla Carta Informativa del Paziente (contenuta nella confezione di Bosentan Sandoz). È importante che lei si sottoponga a questi esami del sangue ad intervalli regolari durante l'intero periodo di assunzione di Bosentan Sandoz. Si consiglia di annotare sulla Carta Informativa del Paziente la data dell'esame più recente e anche quella del prossimo esame previsto (chiedere la data al medico), questo l'aiuterà a ricordare quando deve fare l'esame successivo.

Esami del sangue per la funzione del fegato
Verranno effettuati ogni mese per tutta la durata del trattamento con Bosentan Sandoz. In seguito ad incremento della dose verrà effettuato un esame addizionale dopo 2 settimane.

Esami del sangue per l'anemia
Verranno effettuati ogni mese per i primi 4 mesi del trattamento e successivamente ogni 3 mesi, in quanto i pazienti che assumono Bosentan Sandoz possono sviluppare anemia.

Se questi risultati sono anomali, il medico può decidere di ridurre la dose o sospendere il trattamento con Bosentan Sandoz ed effettuare ulteriori esami per determinarne la causa.

Bambini e adolescenti

Bosentan Sandoz non è raccomandato nei pazienti pediatrici con sclerosi sistemica ed ulcere digitali attive. Bosentan Sandoz non deve essere usato anche nei bambini con peso corporeo inferiore a 31 kg affetti da ipertensione arteriosa polmonare. Vedere anche il paragrafo 3. Come prendere Bosentan Sandoz.

Altri medicinali e Bosentan Sandoz
Informi il medico o il farmacista se sta assumendo, ha recentemente assunto o potrebbe assumere qualsiasi altro medicinale, inclusi i medicinali ottenuti senza prescrizione medica.
È importante, soprattutto, informare il medico se sta prendendo:
- ciclosporina A (un medicinale utilizzato dopo i trapianti e per il trattamento della psoriasi) che non deve essere usato insieme a Bosentan Sandoz
- sirolimus o tacrolimus, che sono medicinali usati dopo trapianti, il cui uso insieme a Bosentan Sandoz non è raccomandato
- glibenclamide [un medicinale per il diabete], rifampicina [un medicinale per la tubercolosi], fluconazolo e ketoconazolo [medicinali per il trattamento di infezioni da funghi], nevirapina [un medicinale per l'HIV], in quanto l'uso di questi medicinali insieme a Bosentan Sandoz non è raccomandato
- altri medicinali per il trattamento dell'infezione da HIV che possono richiedere un monitoraggio speciale se utilizzati insieme al Bosentan Sandoz.
- contraccettivi ormonali, che non sono efficaci come unico metodo di contraccezione quando assume Bosentan Sandoz. All'interno della confezione di Bosentan Sandoz troverà una Carta Informativa del Paziente che dovrà leggere attentamente. Il medico e/o il ginecologo stabilirà il metodo contraccettivo appropriato per lei
- altri medicinali per il trattamento dell'ipertensione polmonare: sildenafil e tadalafil
- warfarin (un agente anticoagulante)
- simvastatina (usata per trattare l'ipercolesterolemia)

Bosentan Sandoz con cibi e bevande
Bosentan Sandoz può essere preso a digiuno o a stomaco pieno.

Gravidanza, allattamento e fertilità
Se è in corso una gravidanza, se sospetta o sta pianificando una gravidanza, o se sta allattando con latte materno, chiedo consiglio al medico o al farmacista prima di prendere questo medicinale.

Donne in età fertile
NON assuma Bosentan Sandoz se lei è in stato di gravidanza o sta cercando di rimanere incinta.

Test di gravidanza
Bosentan Sandoz può nuocere al nascituro concepito prima o durante il trattamento. Se lei è una donna in età fertile, il medico le chiederà di effettuare un test di gravidanza prima di iniziare l'assunzione di Bosentan Sandoz e di effettuarlo, quindi, regolarmente durante il trattamento con Bosentan Sandoz.

Contraccettivi
Se lei è una donna in età fertile, utilizzi un metodo affidabile di controllo della nascita (contraccettivo) mentre prende Bosentan Sandoz. Il medico o ginecologo la consiglierà sui metodi contraccettivi affidabili durante il trattamento con Bosentan Sandoz. Poiché Bosentan Sandoz può rendere inefficace la contraccezione ormonale (ad esempio contraccettivi orali, iniettabili, impiantabili o cerotti cutanei), questo metodo da solo non è affidabile. Quindi, se lei usa contraccettivi ormonali deve usare anche un metodo di barriera (ex. profilattico femminile, diaframma, spugna contraccettiva oppure anche il suo partner deve utilizzare il profilattico). All'interno della confezione di Bosentan Sandoz troverà una Carta Informativa del Paziente. Lei dovrà compilare questa carta e portarla al suo medico alla prossima visita, in questo modo il medico o il ginecologo potranno valutare se lei ha bisogno di metodi contraccettivi addizionali o alternativi affidabili. Si raccomanda di effettuare un test di gravidanza ogni mese durante il trattamento con Bosentan Sandoz se lei è in età fertile.

Informi immediatamente il medico se inizia una gravidanza durante il trattamento con Bosentan Sandoz o se ha intenzione di dare inizio ad una gravidanza nell'immediato futuro.

Allattamento
Informi immediatamente il medico se sta allattando. Si consiglia di interrompere l'allattamento al seno in caso le venga prescritto Bosentan Sandoz in quanto non si sa se questo medicinale viene escreto nel latte materno.

Fertilità
Se lei è un uomo che assume Bosentan Sandoz è possibile che questo medicinale riduca la conta degli spermatozoi. Non si può escludere che questo possa compromettere la possibilità di concepire un figlio. Parli con il medico se ha domande su questo argomento.

Guida di veicoli e utilizzo di macchinari
Bosentan Sandoz può indurre ipotensione (riduzione della sua pressione sanguigna) che può provocarle capogiri, influenzare la sua vista e la sua capacità di guidare veicoli e usare macchinari. Pertanto se lei avverte un senso di vertigine o ha offuscamento della vista durante il trattamento con Bosentan Sandoz, non guidi o non utilizzi strumenti o macchinari di alcun genere.

3. Come prendere Bosentan Sandoz

Prenda questo medicinale seguendo sempre esattamente le istruzioni del medico o del farmacista. Se ha dubbi consulti il medico o il farmacista.

Il trattamento con Bosentan Sandoz deve essere iniziato e monitorato solo da un medico che ha esperienza nel trattamento della PAH o della sclerosi sistemica.

Dose raccomandata

Adulti
Negli adulti il trattamento ha inizio normalmente con l'assunzione di una compressa da 62,5 mg due volte al giorno (mattina e sera) per le prime 4 settimane, in seguito il medico consiglierà solitamente di assumere una compressa da 125 mg due volte al giorno a seconda della risposta a Bosentan Sandoz riscontrata.

Bambini ed adolescenti
La dose raccomandata nei bambini è solo per la PAH. Per bambini di età uguale o maggiore a 1 anno il trattamento con Bosentan Sandoz ha inizio normalmente con l'assunzione di 2 mg per kg di peso corporeo due volte al giorno (mattina e sera). Tuttavia, alcune dosi di bosentan non sono adatte nei bambini con un peso corporeo inferiore a 31 kg. Per questi pazienti è necessario una compressa di bosentan con dosaggio minore. Il dosaggio verrà definito dal medico.
Bosentan è disponibile anche in forma di compresse dispersibili da 32 mg, che possono facilitare il corretto dosaggio nei bambini e nei pazienti con basso peso corporeo a con difficoltà a deglutire le compresse rivestite con film.
Se lei ha l'impressione che gli effetti di Bosentan Sandoz siano troppa forti o troppo deboli, parli con il medico allo scopo di valutare se è necessario cambiare la posologia.

Come prendere Bosentan Sandoz
Assumere le compresse (mattina e sera) deglutendole con acqua. Le compresse possono essere assunte a digiuno o a stomaco pieno.

Se prende più Bosentan Sandoz di quanto deve
Se prende più compresse di quante prescritte, consulti immediatamente il medico.

Se dimentica di prendere Bosentan Sandoz
Se dimentica di assumere Bosentan Sandoz, prenda una compressa non appena si ricorda e poi continui ad assumere le compresse agli orari abituali. Non prenda una dose doppia per compensare la dimenticanza di una compressa.

Se interrompe il trattamento con Bosentan Sandoz
La sospensione improvvisa del trattamento con Bosentan Sandoz può comportare un aggravamento dei sintomi. Non sospenda il trattamento con Bosentan Sandoz se non su indicazione del medico. Il medico può consigliarle di ridurre la dose nell'arco di alcuni giorni prima di sospendere definitivamente il trattamento con Bosentan Sandoz.

Se ha qualsiasi dubbio sull'uso di questo medicinale, si rivolga al medico o al farmacista.

4. Possibili effetti indesiderati

Come tutti i medicinali, questo medicinale può causare effetti indesiderati sebbene non tutte le persone li manifestino.

Gli effetti indesiderati più gravi connessi a Bosentan Sandoz sono:
- Alterazione della funzione del fegato che può interessare più di 1 persona su 10.
- Anemia (riduzione dei valori negli esami del sangue) che può interessare fino a 1 persona su 10. L'anemia, occasionalmente, può necessitare di una trasfusione di sangue.

I valori risultanti dagli esami del fegato e del sangue devono essere monitorati durante il trattamento con Bosentan Sandoz (vedere paragrafo 2). È' importante che lei faccia questi controlli così come prescritto dal medico.

I segni di un non corretto funzionamento del fegato includono:
- nausea (impulso a vomitare)
- vomito
- febbre (temperatura elevata)
- dolori alla stomaco (addome)
- ittero (ingiallimento della pelle o della parte bianca dell'occhio)
- urina di colore scuro
- prurito della pelle

10428

824501

Україна * Товариство з обмеженою відповідальністю «САНДОЗ УКРАЇНА» * м. Київ * ДЛЯ ДОКУМЕНТІВ * 38419586

БОГОЛЕПОВ А.А.

SANDOZ
stylegraph C. 03310/7
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APPROVED
By Oktay ÖZ at 8:07 pm, Apr 20, 2018

- letargia o affaticamento (stanchezza o spossatezza inusuali)
- sindrome simil-influenzale (dolori alle articolazioni e ai muscoli con febbre)

Se nota la comparsa di una di questi segni **informi immediatamente il medico.**

Altri effetti indesiderati.

Molto comuni (possono interessare **più di 1 persona su 10**):
- Mal di testa
- Edema (gonfiore delle gambe e delle caviglie o altri segni dovuti a ritenzione dei liquidi)

Comuni (possono interessare **fino a 1 persona su 10**):
- Aspetto arrossato o arrossamento della pelle
- Reazioni di ipersensibilità (che includono infiammazione della pelle, prurito e eruzione cutanea)
- Malattia da reflusso gastroesofageo (reflusso acido)
- Diarrea
- Sincope (svenimento)
- Palpitazioni (battiti del cuore veloci o irregolari)
- Pressione sanguigna bassa
- Congestione nasale

Non comuni (possono interessare **fino a 1 persona su 100**):
- Trombocitopenia (basso numero di piastrine nel sangue)
- Neutropenia/leucopenia (basso numero di globuli bianchi)
- Alterazioni negli esami di funzionalità epatica associate a epatite (infiammazione del fegato) inclusa possibile esacerbazione dell'epatite esistente e/o ittero (ingiallimento della cute o della parte bianca dell'occhio)

Rari (possono interessare **fino a 1 persona su 1000**):
- Anafilassi (reazione allergica generalizzata), angioedema (gonfiore, più comune intorno ad occhi, labbra, lingua o gola)
- Cirrosi (cicatrizzazione) del fegato, insufficienza epatica grave (grave disturbo della funzionalità del fegato)

È stato segnalato anche offuscamento della vista con una frequenza non nota (la frequenza non può essere definita sulla base dei dati disponibili).

Effetti indesiderati aggiuntivi nei bambini e adolescenti
Gli effetti indesiderati che sono stati riportati nei bambini trattati con Bosentan Sandoz sono gli stessi di quelli degli adulti.

Segnalazione degli effetti indesiderati
Se manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio, si rivolga al medico o al farmacista. Lei può inoltre segnalare gli effetti indesiderati direttamente tramite il sistema nazionale di segnalazione all'indirizzo www.aifa.gov.it/content/segnalazioni-reazioni-avverse. Segnalando gli effetti indesiderati lei può contribuire a fornire maggiori informazioni sulla sicurezza di questo medicinale.

5. Come conservare Bosentan Sandoz

Conservi questo medicinale fuori dalla vista e dalla portata dei bambini.

Non usi questo medicinale dopo la data di scadenza che è riportata sulla scatola e sul blister dopo Scad. La data di scadenza si riferisce all'ultimo giorno di quel mese.

Questo medicinale non richiede alcuna condizione particolare di conservazione.

Non getti alcun medicinale nell'acqua di scarico e nei rifiuti domestici. Chieda al farmacista come eliminare i medicinali che non utilizza più. Questo aiuterà a proteggere l'ambiente.

6. Contenuto della confezione e altre informazioni

Cosa contiene Bosentan Sandoz

Bosentan Sandoz 62,5 mg compresse rivestite con film: il principio attivo è il bosentan (come monoidrato).

Ogni compressa contiene 62,5 mg di bosentan (corrispondenti a 64,541 mg di bosentan monoidrato).

Bosentan Sandoz 125 mg compresse rivestite con film: il principio attivo è il bosentan (come monoidrato).

Ogni compressa contiene 125 mg di bosentan (corrispondenti a 129,082 mg di bosentan monoidrato).

Gli altri componenti all'interno della compressa sono: amido di mais, amido di mais pregelatinizzato, sodio amido glicolato tipo A, povidone K30, poloxamer 188, silice colloidale anidra, glicerolo dibenato e magnesio stearato.

Il rivestimento in film contiene Opadry Orange 21K23007 (contenente ipromellosa, titanio diossido, esticellulosa, triacetino, talco, ferro ossido giallo (E172), ferro ossido rosso (E172), ferro ossido nero (E172).

Descrizione dell'aspetto di Bosentan Sandoz e contenuto della confezione

Bosentan Sandoz 62,5 mg compresse rivestite con film sono compresse rivestite con film di colore arancione chiaro, rotonde, biconvesse di 6 mm di diametro

Bosentan Sandoz 125 mg compresse rivestite con film sono compresse rivestite con film di colore arancione chiaro, ovali, biconvesse di dimensioni 11 mm x 5 mm.

Blister PVC/PVDC/Alluminio contenenti 14 compresse rivestite con film.

Le scatole contengono 14, 56 o 112 compresse rivestite con film

E' possibile che non tutte le confezioni siano commercializzate.

Titolare dell'autorizzazione all'immissione in commercio

Sandoz S.p.A.
Lgo U. Boccioni 1, 21040 Origgio (VA)
Italia

Produttore

GE Pharmaceuticals Ltd.
Industrial Zone, 'Chekanitza-South' area, Botevgrad 2140
Bulgaria

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana
Slovenia

Questo medicinale è autorizzato negli Stati Membri dello Spazio Economico Europeo con le seguenti denominazioni:

Paesi Bassi	Bosentan Sandoz 62.5 mg, filmomhulde tabletten Bosentan Sandoz 125 mg, filmomhulde tabletten
Austria	Bosentan Sandoz 62.5 mg, Filmtabletten Bosentan Sandoz 125 mg, Filmtabletten
Belgio	Bosentan Sandoz 62.5 mg, filmomhulde tabletten Bosentan Sandoz 125 mg, filmomhulde tabletten
Bulgaria	Bosentan Sandoz 62.5 mg Филмирана таблетка Bosentan Sandoz 125 mg Филмирана таблетка
Repubblica Ceca	Bosentan Ebewe
Germania	Bosentan HEXAL 62.5 mg, Filmtabletten Bosentan HEXAL 125 mg, Filmtabletten
Spagna	Bosentan Sandoz Farmaceutico 62.5 mg, comprimidos recubiertos con película EFG Bosentan Sandoz Farmaceutico 125 mg, comprimidos recubiertos con película EFG
Finlandia	Bosentan Sandoz 62.5 mg, tabletti, kalvopäällysteinen Bosentan Sandoz 125 mg, tabletti, kalvopäällysteinen
Francia	BOSENTAN SANDOZ 62.5 mg, comprimé pelliculé BOSENTAN SANDOZ 125 mg, comprimé pelliculé
Italia	Bosentan Sandoz
Lettonia	Bosentan Welding 62.5 mg, apvalkotās tabletes Bosentan Welding 125 mg, apvalkotās tabletes
Norvegia	Bosentan Sandoz 62.5 mg, tablett, filmdrasjert Bosentan Sandoz 125 mg, tablett, filmdrasjert
Polonia	Bosentan Sandoz Gmbh 62,5 mg tabletki powlekane Bosentan Sandoz Gmbh 125 mg tabletki powlekane
Portogallo	Bosentano Sandoz
Romania	Bosentan Sandoz 62.5 mg, comprimate filmate Bosentan Sandoz 125 mg, comprimate filmate
Svezia	Bosentan Sandoz 62.5 mg, filmdragerad tablett Bosentan Sandoz 125 mg, filmdragerad tablett
Slovacchia	Bosentan Sandoz 62.5 mg Bosentan Sandoz 125 mg

Questo foglio illustrativo è stato aggiornato il 03/2018

CARTA INFORMATIVA DEL PAZIENTE

Informazioni importanti sulla Sicurezza per i Pazienti che assumono Bosentan Sandoz

Questa scheda contiene informazioni importanti su Bosentan Sandoz. Legga questa scheda attentamente prima di iniziare il trattamento con bosentan.

Nome: _____
Medico prescrittore: _____
Rivolgersi al medico in caso si abbiano domande relative a Bosentan Sandoz.

Sandoz S.p.A.

Se lei è una donna in età fertile, legga questa pagina con attenzione

Gravidanza

Bosentan Sandoz può danneggiare lo sviluppo del feto. Quindi lei non deve assumere Bosentan Sandoz se è in gravidanza e non deve iniziare una gravidanza mentre assume Bosentan Sandoz.

Inoltre, se lei soffre di ipertensione polmonare, la gravidanza può aggravare severamente i sintomi della malattia. Se lei sospetta di poter essere in gravidanza, lo dica al suo medico o ginecologo.

Contraccezione

La contraccezione di tipo ormonale - come i contraccettivi orali e pillole contraccettive, ormoni iniettabili, impianti o cerotti cutanei contraccettivi, non prevengono in maniera affidabile la gravidanza nelle donne che assumono Bosentan Sandoz. Lei ha bisogno di usare un metodo di barriera contraccettivo – come il profilattico, il diaframma o la spugna vaginale – in aggiunta a ciascuno di questi tipi di contraccettivi ormonali. Si assicuri di discutere ogni possibile domanda con il suo medico o con il ginecologo – compilari i dati richiesti sul retro di questa scheda e la porti al suo medico o ginecologo alla prossima visita.

Lei deve effettuare un test di gravidanza prima di iniziare Bosentan Sandoz e ogni mese durante il trattamento anche se pensa di non essere in gravidanza.

Data del primo test mensile: _____

Contraccezione

Lei abitualmente prende o usa contraccettivi
☐ Sì ☐ No

Se sì, scriva i loro nomi qui:
_____
_____

Porti questa scheda al suo medico o ginecologo alla prossima visita e lui/lei sarà in grado di consigliarla sulla necessità di usare metodi contraccettivi addizionali o alternativi.

Analisi del sangue per la funzione epatica

È stato riscontrato che alcuni pazienti sottoposti al trattamento con Bosentan Sandoz presentavano esiti anomali negli esami per la funzionalità epatica. Durante il trattamento con Bosentan Sandoz il medico provvederà a richiedere esami del sangue al fine di controllare con regolarità eventuali cambiamenti della funzionalità epatica.

Si ricordi di fare ogni mese l'esame del sangue per la funzionalità epatica. A seguito di un aumento della dose, verrà effettuato un esame addizionale dopo 2 settimane.

Data del primo esame mensile: _____

Il suo programma mensile di analisi del sangue per il fegato:

☐ Gen	☐ Mag	☐ Set
☐ Feb	☐ Giu	☐ Ott
☐ Mar	☐ Lug	☐ Nov
☐ Apr	☐ Ago	☐ Dic

PRODUCT INFORMATION
BOSENTAN SANDOZ 62.5 mg and 125 mg tablets

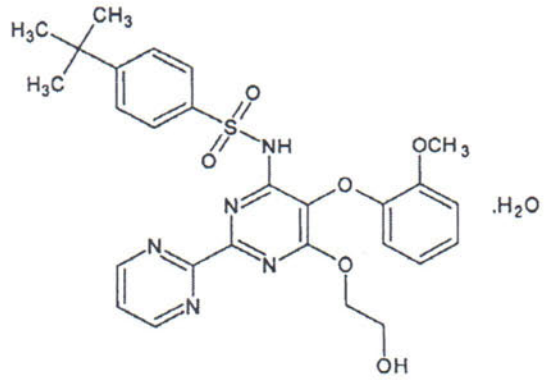
Bosentan may cause birth defects and is contraindicated in pregnancy.
See CONTRAINDICATIONS and PRECAUTIONS.
Rare cases of hepatic cirrhosis and hepatic failure have been reported in patients using Bosentan. See PRECAUTIONS

NAME OF THE MEDICINE

Active: Bosentan (as monohydrate)

The chemical name of Bosentan monohydrate is benzenesulphonamide, 4-(1,1 -dimethylethyl)-N-[6-(2hydroxyethoxy)-5-(2-methoxyphenoxy) [2,2'- bipyrimidin]-4-yl]-, monohydrate.

The structural formula is:



The molecular formula is:

$C_{27}H_{29}N_5O_6S$	Anhydrous MW: 551.62
$C_{27}H_2{}_9N_5O_6S.H_2O$	Monohydrate MW: 569.64
CAS	147536-97-8 (anhydrous substance)

Bosentan is the first of a new drug class, an endothelin receptor antagonist. Bosentan belongs to a class of highly substituted pyrimidine derivatives, with no chiral centres.

DESCRIPTION

Bosentan monohydrate, a white to off-white powder, is practically insoluble at low pH (0.1 mg/100 mL at pH 1.1 and 4.0; 0.2 mg/100 mL at pH 5.0).
Solubility increases at higher pH values (43 mg/100 mL at pH 7.5). In the solid state, bosentan monohydrate is very stable, is not hygroscopic and shows no light sensitivity.

Each Bosentan Sandoz 62.5 mg film tablet contains 62.541 mg/tablet bosentan (as monohydrate), equivalent to 62.5 mg bosentan.

Each Bosentan Sandoz 125 mg film tablet contains 129.082 mg/tablet bosentan (as monohydrate), equivalent to 125 mg bosentan.

Bosentan Sandoż tablets also contain the following inactive ingredients: maize starch, pregelatinised maize starch, sodium starch glycollate type A, povidone, polaxamer, silica colloidal anhydrous, glycerol dibenhyate, magnesium stearate, hydroxypropyl methyl cellulose, titanium dioxide, ethyl cellulose, triacetin, talc, Yellow Iron Oxide, Red Iron Oxide and Black Iron Oxide.

PHARMACOLOGY

Pharmacodynamic Properties

The neurohormone endothelin-1 (ET-1) is a potent vasoconstrictor. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension (PAH) suggesting a pathogenic role for ET-1 in this disease.

Bosentan is a specific and competitive antagonist at endothelin receptor types ETA and ETB. Bosentan has a slightly higher affinity for ETA receptors than for ETB receptors.

Pharmacokinetics

General

After oral administration, maximum plasma concentrations of bosentan found in a study of the 125 mg tablets taken as a single dose, were attained within 3.7 ± 1.7 hours and the apparent elimination half-life ($t_{1/2}$) was 5.6 ± 1.6 hours in 16 fasted subjects. The pharmacokinetics of oral bosentan have not been studied in patients with PAH. The clearance of intravenous bosentan was significantly lower in patients with primary pulmonary hypertension (PPH) (3.8 L/h) than in healthy volunteers (9 L/h). Exposure is also expected to be greater in patients with PAH since increased (30-40%) bosentan exposure has been observed in patients with severe chronic heart failure.

Absorption and Distribution

In healthy volunteers at a dose of 600 mg, the absolute bioavailability of bosentan from an oral suspension was 41%. At a dose of 125 mg, administration of bosentan with food did not have a significant effect on the extent of absorption but did increase the rate, leading to a 20% increase in peak plasma concentrations of bosentan. This is not expected to be clinically significant. The volume of distribution and clearance of bosentan are non-linear and decrease as the dose increases. The mean volume of distribution of 17.8 ± 3.6 L/h and the mean clearance of 8.8 ± 1.9 L were determined after a mean IV dose of 250 mg was administered to 18 healthy male volunteers. Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin.
Bosentan does not penetrate into erythrocytes.

Metabolism and Elimination
Bosentan is metabolised in the liver by the cytochrome P450 enzymes, CYP2C9 and CYP3A4, and eliminated by biliary excretion. 94% of a radioactive oral dose was recovered in faeces (30% was unchanged). Bosentan has three metabolites, one of which is pharmacologically active and may contribute 20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19. Total clearance after a single intravenous dose is about 8 L/hr. Upon multiple dosing, plasma concentrations decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolising liver enzymes. Steady state is reached within 3-5 days. Less than 3% of an administered oral dose is recovered in urine.

Special Populations
It is not known whether bosentan pharmacokinetics are influenced by gender, body weight, race, or age.

Hepatic Function Impairment
The steady-state pharmacokinetics of bosentan and metabolites were studied in 8 patients with mild hepatic impairment (Child-Pugh Class A) without pulmonary hypertension. Compared to healthy controls, bosentan C_{max}, AUC and half-life were not significantly altered; AUC of the active metabolite Ro 48-5033 was increased by 33%; trough concentrations of Ro 48-5033 and Ro 64-1056 were increased by 75% and 20%, respectively. Based on these findings, no dosage adjustment is required in patients with mild hepatic impairment (see DOSAGE AND ADMINISTRATION).

The pharmacokinetics of bosentan have not been studied in patients with moderate to severe hepatic impairment. Bosentan is contraindicated in patients with moderate to severe hepatic abnormalities and/or baseline elevated aminotransferases > 3 x Upper Limit of Normal (ULN) (see CONTRAINDICATIONS).

Renal Impairment
In patients with severe renal impairment (creatinine clearance 15-30 mL/min), plasma concentrations of bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2-fold compared to people with normal renal function. These differences do not appear to be clinically important (see DOSAGE AND ADMINISTRATION).

Children
The pharmacokinetics of bosentan at steady-state were studied in 19 children aged 3 to 15 years with PPH or PAH secondary to congenital systemic to pulmonary communications. The number of patients studied in each dose group was insufficient to establish the optimal dosing regimen. In children weighing over 20 kg, administration of the recommended dose regimen (see DOSAGE AND ADMINISTRATION) led to bosentan plasma concentrations which were higher than those in healthy adults taking the recommended adult dose, but similar to those expected in adults with pulmonary hypertension. In children weighing 10-20 kg, bosentan plasma concentrations during administration of the recommended dose were lower than in healthy adults, and thus lower than those expected in adults with pulmonary hypertension. However, the recommended dose was associated with

haemodynamic improvement and should not be exceeded on safety grounds. The steady-state half-life of bosentan in children averaged 5 to 6 hours.

CLINICAL TRIALS

Adult Patients with Pulmonary Arterial Hypertension (PAH)

WHO Grade Functional Class III & IV

Two randomised, double-blind, multicentre, placebo-controlled trials were conducted in 32 and 213 patients. The larger study (BREATHE-1, Study 352) compared the two bosentan doses pooled (125 mg twice daily and 250 mg twice daily) of bosentan with placebo. The smaller study (Study 351) compared bosentan 125 mg twice daily with placebo.

Patients had severe (WHO Functional Class III-IV) PAH: PPH (72%) or pulmonary hypertension secondary to scleroderma or other connective tissue diseases (21%), or to autoimmune disease (7%). There were no patients with pulmonary hypertension secondary to HIV, or pulmonary embolus.

In both studies, bosentan or placebo was added to patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, and vasodilators (e.g. calcium channel blockers, ACE inhibitors), but not epoprostenol. Bosentan was given at a dose of 62.5 mg twice daily for 4 weeks and then at 125 mg twice daily or 250 mg twice daily for either 12 (BREATHE-1) or 8 (Study 351) additional weeks. The primary study endpoint was 6-minute walking distance. In addition, symptoms and functional status were assessed. Haemodynamic measurements were made at 12 weeks in Study 351. The exploratory analysis of these prospectively defined secondary parameters showed results that are consistent with the results for the primary parameter.

The mean age was about 49 years. About 80% of patients were female, and about 80% were Caucasian. Patients had been diagnosed with pulmonary hypertension for a mean of 2.4 years.

Submaximal Exercise Capacity

Results of the 6-minute walk distance at 3 months (Study 351) or 4 months (BREATHE-1) are shown in Table 1.

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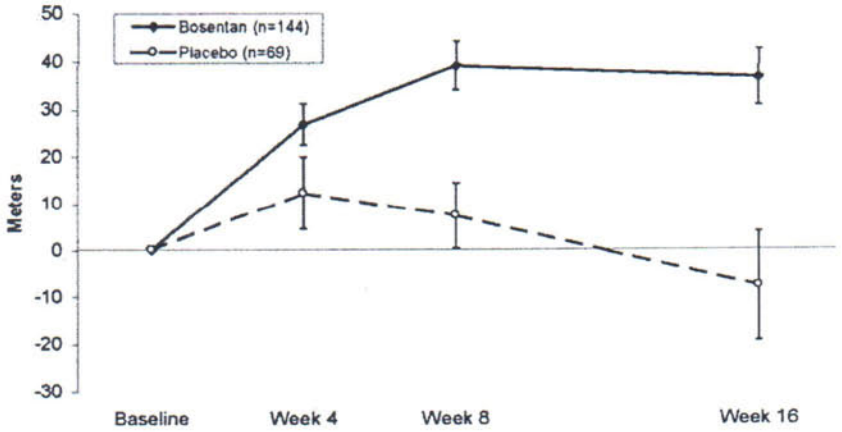
Table 1: Effects of Bosentan on 6-minute walk

	BREATHE-1		Study 351	
	125/250 mg twice daily	Placebo	125 mg twice daily	Placebo
N	144	69	21	11
Baseline	330 ± 74	344 ± 76	360 ± 86	355 ± 82
Endpoint	366 ± 109	336 ± 130	430 ± 66	350 ± 147
Change from Baseline	36 ± 70	-8 ± 96	70 ± 56	-6 ± 120
Placebo-subtracted	44**	-	76*	-

Distance in metres: mean ±SD
Changes are to Week 16 for BREATH-1 and Week 12 for Study 351.
**p=0.0002 for 125 mg and 250 mg doses combined by Wilcoxon test
*p=0.02 by Student's t-test

In both trials, treatment with bosentan resulted in a significant increase in exercise capacity. The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg twice daily) and fully developed by about 2 months of treatment (Figure 1). It was maintained for up to 7 months of double-blind treatment. The placebo-subtracted mean increase in walking distance was somewhat greater with 250 mg twice daily (54 m) than with 125 mg twice daily (35 m). However, the higher dose is not recommended because of the potential for increased liver injury (see DOSAGE AND ADMINISTRATION).

Figure 1: Mean Change in 6-min Walk Distance (BREATHE-1)



Change from baseline in 6-minute walking distance from start of therapy to week 16 in the placebo and combined bosentan (125 mg and 250 mg twice daily) groups. Values are expressed as mean ± standard error of the mean.

There were no apparent differences in treatment effects on walk distance among subgroups analysed by demographic factors, baseline disease severity, or disease aetiology, but the studies had little power to detect such differences.

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Haemodynamic Changes
Invasive haemodynamic parameters were assessed in Study 351. Treatment with bosentan led to a significant increase in cardiac index (CI) associated with a clinically relevant reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and mean right atrial pressure (RAP) (Table 2).

Table 2: Change from Baseline to Week 12: Haemodynamic Parameters

	Bosentan		**Placebo**
Mean CI (L/min/m^2)	n=20		n=10
Baseline	2.35 ± 0.16		2.48 ± 0.33
Absolute Change	0.50 ± 0.10		-0.52 ± 0.15
Treatment Effect		1.02 ± 0.18***	
Mean PAP (mmHg)	n=20		n=10
Baseline	53.7 ± 3.0		55.7 ± 3.3
Absolute Change	-1.6 ± 1.2		5.1 ± 2.8
Treatment Effect		-6.7 ± 2.5**	
Mean PVR (dyn.sec.cm^{-5})	n=19		n=10
Baseline	896 ± 97		942 ± 136
Absolute Change	-223 ± 56		191 ± 74
Treatment Effect		-415 ± 94**	
Mean RAP (mmHg)	n=19		n=10
Baseline	97 ± 1.3		9.9 ± 1.3
Absolute Change	-1.3 ± 0.9		4.9 ± 1.5
Treatment Effect		-6.2 ± 1.7***	

Values shown are means ±SE
** p< 0.02
*** p≤ 0.001

Symptoms and Functional Status
Symptoms of PAH were assessed by Borg Dyspnoea score, WHO functional class, and rate of "clinical worsening". In Study 351, clinical worsening was defined as death from all causes, lung transplantation or discontinuation of therapy due to clinical deterioration. In the BREATHE-1 study, clinical worsening was assessed as death from all causes, transplantation, hospitalisations or discontinuation of therapy due to worsening of PAH, need for prostacyclin or septostomy. There was a clinically relevant reduction in dyspnoea during walk tests (Borg Dyspnoea score), and clinically relevant improvement in WHO functional class in bosentan-treated patients. There was a clinically relevant reduction in the rate of clinical worsening (Table 3).

Table 3: Incidence of Clinical Worsening, Intent to Treat Population				
	BREATHE-1		**Study 351**	
	Bosentan 125/250 mg twice daily (n=144)	Placebo (n=69)	Bosentan 125 mg twice daily (n=21)	Placebo (n=11)
Patients with clinical worsening[n (%)]	9 (6)*	14 (20)	0 (0)**	3 (27)
-Death	1 (1)	2 (3)	0 (0)	0 (0)
-Hospitalisation for PAH	6 (4)	9 (13)	0 (0)	3 (27)
-Discontinuation due to worsening of PAH	5 (3)	6 (9)	0 (0)	3 (27)
-Receipt of epoprostenol***	4 (3)	3 (4)	0 (0)	3 (27)

Note: Patients may have had more than one reason for clinical worsening.
* p=0.0015 vs. placebo by log-rank test. There was no observed difference between the 125 mg and 250 mg twice daily groups.
** p=0.033 vs. placebo by Fisher's exact test.
*** Receipt of epoprostenol was always a consequence of clinical worsening.
PAH = pulmonary arterial hypertension.

There are limited data available on the minimum effective dose, dose response, and the clinically useful dose-range for bosentan.

There are no studies to demonstrate beneficial effects on survival of treatment with bosentan. However, long-term vital status was recorded for all 235 patients who were treated with bosentan in the two pivotal placebo-controlled trials (AC-052-351 and AC-052-352) and/or their two uncontrolled, open-label extensions. The mean duration of exposure to bosentan was 1.9 years ± 0.7 years; [min: 0.1; max: 3.3 years] and patients were observed for a mean of 2.0 ± 0.6 years. The majority of patients were diagnosed as PPH (72%) and were in WHO functional class III (84%). In this total population, Kaplan-Meier estimates of survival were 93% and 84% after 1 and 2 years after the start of treatment with bosentan, respectively. Survival estimates were lower in the subgroup of patients with PAH secondary to systemic sclerosis. The estimates may have been influenced by the initiation of epoprostenol treatment in 43/235 patients.

WHO Grade Functional Class II
In a randomised, double-blind, multi-centre, placebo-controlled trial (AC-052-364:EARLY) 185 PAH patients in WHO functional class II (mean baseline 6- minute walk distance of 435 metres) received bosentan 62.5 mg b.i.d. for 4 weeks followed by 125 mg b.i.d. (n=93), or placebo (n=92) for 6 months. Patients were diagnosed with idiopathic/familial PAH (n= 112), PAH associated with connective tissue disease (n=34), congenital heart disease (n=32) or other (n=7). Enrolled patients were PAH-treatment naive (n=156) or on a stable dose of sildenafil (n=29). EARLY was designed as a superiority study with co-primary endpoints of percentage change from baseline in PVR, and change from baseline in 6-minute walk distance to 6 months versus placebo. Secondary endpoints included time to clinical worsening, Borg dyspnoea score, WHO functional class, and quality of life. With 85 patients per treatment group, a ≥ 20% reduction in the geometric mean PVR and a ≥ 35-metre increase in the mean 6-minute walk distance in the active vs placebo group could be detected with > 99% and 91% power, respectively. The two primary endpoints were

evaluated hierarchically, with the endpoint on walk distance tested only if the endpoint regarding PVR was significant, with both tested at a two-sided type-I error of 0.05. The main analysis was on the all-randomised analysis set.

The table below illustrates the outcomes in the main analysis of the two primary endpoints

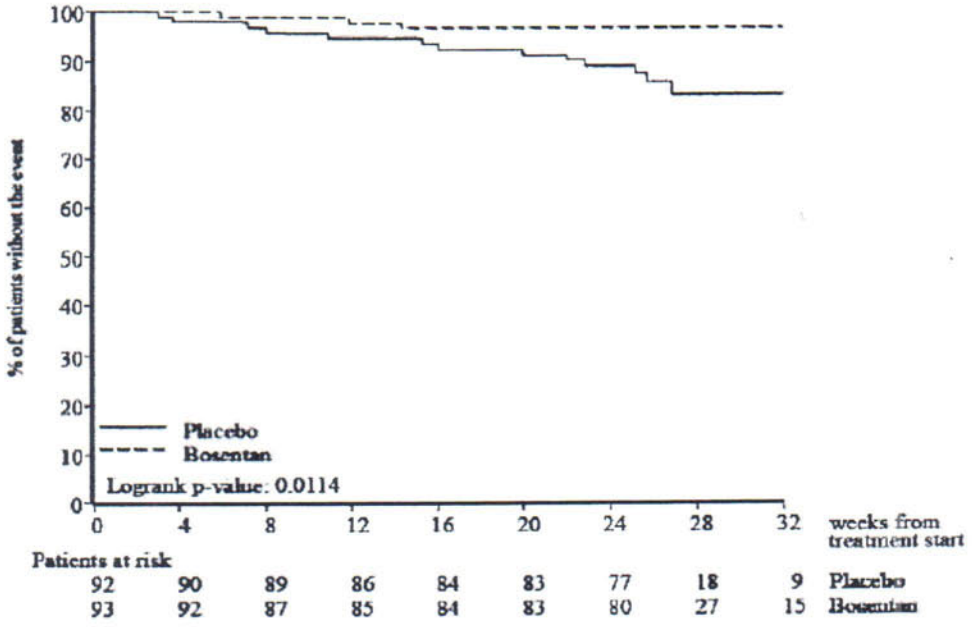
Table 4: Percentage change from baseline to 6 months bosentan versus placebo for co-primary endpoints (PVR and 6-minute Walk Distance)

	PVR (dyn.sec/cm^5)		6-Minute Walk distance (m)	
	Placebo (n=88)	Bosentan (n=80)	Placebo (n=91)	Bosentan (n=86)
Baseline (BL); mean (SD)	802 (365)	851 (535)	431 (92)	443 (83)
Change from BL; mean (SD)	128 (465)	-69 (475)	-8 (79)	11 (74)
Treatment effect	-22.6%		19	
95% CL	-34, -10		-4, 42	
p-value	< 0.0001		0.0758	

Patients with WHO functional class II PAH, on average, have only moderately impaired 6MWT and may therefore have a limited response range for improvement in this parameter. This could partly explain the lack of statistical significance for the 6MWT endpoint. However, there was a clear association between an absence of deterioration from baseline in 6MWT and stable WHO functional class in the EARLY population. No patient in the bosentan group who at least maintained baseline 6MWT had deterioration in functional class.

Treatment with bosentan was associated with a reduction in the rate of clinical worsening (see Figure 2), defined as a composite of symptomatic progression, hospitalisation for PAH and death compared with placebo (proportional risk reduction 77%, 95% CI 20%-94%, p=0.0114).The treatment effect was driven by improvement in the component symptomatic progression (defined as appearance or worsening of right heart failure, ≥ 10% decrease from baseline in two 6-minute walk tests performed ≥ 2 weeks apart, or ≥ 5% decrease from baseline in two 6-minute walk tests performed ≥ 2 weeks apart associated with a ≥ 2-point increase in Borg dyspnoea index). There was one hospitalisation related to PAH worsening in the bosentan group and 3 hospitalisations in the placebo group. There was one death in each treatment group during the 6 month double-blind study period.

Figure 2: EARLY: Kaplan-Meier estimates of time to clinical worsening, all randomised set



Patients are censored at the end of the treatment period.

The EARLY study was designed and powered to evaluate the efficacy of bosentan in the patient population as a whole and was not powered to show statistical significance for each aetiological sub-group. No criteria to determine aetiological subgroup numbers or specific claims of a beneficial effect by subgroup were pre-specified. Subgroup analyses of treatment effects according to PAH aetiology were performed in the EARLY trial with the objective being to support absence of heterogeneity in treatment response between subgroups. For both co-primary endpoints the confidence intervals for treatment effects were overlapping between the major aetiological subgroups. The inclusion criteria for EARLY permitted recruitment of any patient with PAH determined to be idiopathic/familial or secondary to congenital heart defect, or connective tissue disease and other predefined aetiologies. For patients with congenital heart disease the defect had to be isolated and restrictive with no reverse shunt (atrial septum defect (ASD) < 2 cm, ventricular septum defect (VSD) < 1 cm or patent ductus arteriosus (PDA)). The population eventually enrolled reasonably reflected the relative incidences of PAH aetiologies seen in the real world setting. Consequently there was more data available for analysis in the most prevalent aetiological subgroups of idiopathic/familial PAH compared with the other subgroups.

Long-term data were generated from all 173 patients who were treated with bosentan in the controlled phase and/or were switched from placebo to bosentan in the open-label extension phase of the EARLY study. The mean duration of exposure to bosentan treatment was 3.6 ± 1.8 years (up to 6.1 years), with 73% of patients treated for at least 3 years and 62% for at least 4 years. Patients could receive additional PAH treatment as required in the open-label extension. The majority of patients were diagnosed with idiopathic or heritable PAH (61%). Exercise capacity (6 minute walk

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distance) was maintained over the duration of bosentan treatment (mean change from baseline to end of treatment -3.7 m).
Overall, 78% of patients remained in WHO functional class I or II. Kaplan-Meier estimates of survival were 90% and 85% at 3 and 4 years after the start of treatment, respectively. At the same timepoints, 88% and 79% of patients remained free from PAH worsening (defined as all-cause death, lung transplantation, atrial septostomy or start of intravenous or subcutaneous prostanoid treatment). The relative contributions of previous placebo treatment in the double-blind phase and of other medications started during the open-label extension period are unknown.

Study Performed in Children with PAH
One study has been conducted in children with pulmonary hypertension. Bosentan has been evaluated in an open-label non-controlled study in 19 paediatric patients with (PAH) (AC-052-356, BREATHE-3: PPH 10 patients and PAH related to congenital heart diseases 9 patients). This study was primarily designed as a pharmacokinetic study. Patients were divided into and dosed according to three body-weight groups for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the trial. The age range was 3-15 years. Patients were in WHO functional class II (n=12 patients, 79%) or class III (n=4 patients, 21%) at baseline.

Haemodynamics were measured in 17 patients. The mean increase from baseline in cardiac index was 0.51/min/m^2, the mean decrease in mean pulmonary arterial pressure was 8 mmHg, and the mean decrease in pulmonary vascular resistance was 389 dyn.sec.cm^{-5}. These haemodynamic improvements from baseline were similar with or without co-administration of epoprostenol. Changes in exercise test parameters at Week 12 from baseline were highly variable and none were significant. The mean distance travelled in a 6 minute walk test decreased in the sub-group of children with CHD.

PAH associated with Eisenmenger's physiology
In a prospective, multi-centre, randomised, double-blind, placebo-controlled study (BREATHE-5), patients with PAH WHO Class III and Eisenmenger physiology associated with congenital heart disease received bosentan 62.5 mg bid for 4 weeks, then 125 mg bid for a further 12 weeks (n=37, of whom 31 had a predominantly right to left, bidirectional shunt). Patients with ductus arteriosus were excluded. The primary objective was to show that bosentan did not worsen hypoxaemia. After 16 weeks, the mean oxygen saturation was increased in the bosentan group by 1.0% (95% CI -0.7; -2.8%) as compared to the placebo group (n=17 patients), showing that bosentan did not worsen hypoxaemia. The mean pulmonary vascular resistance was significantly reduced in the Bosentan group (with a predominant effect observed in the subgroup of patients with bidirectional intracardiac shunt). After 16 weeks, the mean placebo-corrected increase in 6- minute walk distance was 53 metres (p=0.0079) reflecting improvement of exercise capacity (see PRECAUTIONS).
In the OL extension study (AC-052-409) of AC-052-405 (BREATHE-5) in patients with PAH WHO functional class III and Eisenmenger physiology associated with congenital heart disease, 26 patients continued to receive bosentan during a 24-week treatment period (mean 24.4 ± 2.0 weeks). The effects of bosentan demonstrated in

the double-blind treatment period were generally maintained during longer term treatment (a total treatment period of 40 weeks).

Combination with Epoprostenol
The combination of bosentan and epoprostenol has been investigated in two studies: AC-052-355 (BREATHE-2) and AC-052-356 (BREATHE-3). AC-052-355 was a multi-centre, randomised, double-blind, parallel-group trial of bosentan versus placebo in 33 patients with severe PAH who were receiving concomitant epoprostenol therapy. AC-052-356 was an open-label, non-controlled trial; 10 of the 19 paediatric patients were on concomitant bosentan and epoprostenol therapy during the 12-week trial. The safety profile of the combination was not different from the one expected with each component and the combination therapy was well tolerated in children and adults. The clinical benefit of the combination has not been demonstrated.

INDICATIONS

Bosentan is indicated for the treatment of

- idiopathic pulmonary arterial hypertension
- familial pulmonary arterial hypertension
- pulmonary arterial hypertension associated with scleroderma or
- pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology

in patients with WHO functional Class II, III or IV symptoms

CONTRAINDICATIONS

Pregnancy: Pregnancy category X
Women who are pregnant or who are likely to become pregnant: Bosentan is expected to cause fetal harm if administered to pregnant women (see PRECAUTIONS - Use in Pregnancy). Pregnancy must be excluded before the start of treatment with bosentan and prevented thereafter by use of reliable contraception such as double-barrier contraception. It has been demonstrated that hormonal contraceptives, including oral, injectable, transdermal and implantable contraceptives may not be reliable in the presence of bosentan and should not be used as the sole contraceptive method in patients receiving bosentan. Double barrier contraception is recommended (see INTERACTIONS WITH OTHER MEDICINES: Hormonal contraceptives, including oral, injectable, transdermal and implantable contraceptives). Input from a gynaecologist or similar expert on adequate contraception should be sought as needed.

Bosentan should be started only in patients known not to be pregnant. Women must not become pregnant for at least three months after stopping treatment with bosentan. For female patients of childbearing potential, a prescription for bosentan should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed on the second day of the last normal menstrual period or 11 days after the last unprotected act of sexual intercourse, whichever is later. Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking bosentan.

Україна Товариство з обмеженою відповідальністю САНДОЗ УКРАЇНА м. Київ 39586 ДЛЯ ДОКУМЕНТІВ

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The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and the fetus.

Moderate or Severe Hepatic Impairment
Bosentan is contraindicated in patients with moderate or severe hepatic function impairment (Child Pugh Class B or C and/or baseline elevated aminotransferases > 3 x ULN). The risk of hepatotoxicity is increased in these patients and monitoring liver injury may be more difficult. Elimination of bosentan and its metabolites would also be markedly impaired in such patients (see PHARMACOLOGY, PRECAUTIONS - Potential Liver Injury and Hepatic Impairment, and DOSAGE AND ADMINISTRATION).

Cyclosporine A
Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of bosentan and cyclosporine A is contraindicated.

Glibenclamide
An increased risk of liver enzyme elevations was observed in patients receiving glibenclamide concomitantly with bosentan. Therefore co-administration of glibenclamide and bosentan is contraindicated.

Hypersensitivity
Bosentan is also contraindicated in patients who are hypersensitive to bosentan or any component of the medication.

PRECAUTIONS
Potential Liver Injury
Elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) by more than 3 x ULN were observed in 11% of 658 bosentan-treated patients compared to 2% of 280 placebo-treated patients. Three-fold increases were seen in 12% of 188 PAH patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 4% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥ 3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases) and increases in total bilirubin has in many cases indicated potential for serious liver injury.

Bosentan has been associated with dose-related, and treatment duration-related, elevations in liver aminotransferases, i.e. AST and ALT. These elevations in aminotransferases may reverse spontaneously while continuing treatment with the maintenance dose of bosentan or after dose reduction, but interruption or cessation may be necessary. In the clinical programme, liver enzyme changes generally occurred within the first 26 weeks of treatment but may also occur late in treatment. These increases usually developed gradually, and were mainly asymptomatic, but

some patients also reported abdominal pain, fever, fatigue or flu-like syndrome. The liver enzyme elevations returned, in 97% of cases during the clinical programme, to pre-treatment levels, without sequelae, within a few days to 9 weeks either spontaneously or after dose reduction or discontinuation. In the post-marketing period rare cases of liver cirrhosis and liver failure have been reported.

The increases in liver aminotransferases may partly be due to competitive inhibition of the elimination of bile salts from hepatocytes but other mechanisms, which have not been clearly established, are probably also involved in the occurrence of liver dysfunction. The accumulation of bosentan in hepatocytes leading to cytolysis with potentially severe damage of the liver, or an immunological mechanism, are not excluded. Liver dysfunction risk may also be increased when medicinal products that are inhibitors of the bile salt export pump (BSEP), e.g. rifampicin, glibenclamide and cyclosporine A, are co-administered with bosentan, but limited data are available.

Elevations in gamma-glutamyl transferase (GGT) were observed in 11% of bosentan-treated patients. Elevations in bilirubin or alkaline phosphatase were less common (bilirubin: bosentan 0.4% vs placebo 2.4%; alkaline phosphatase: bosentan 1.9% vs placebo 1.9%). Few patients developed jaundice.

Liver aminotransferase levels must be measured prior to initiation of treatment and monthly thereafter. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated (see DOSAGE AND ADMINISTRATION). If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, lethargy, fatigue, abdominal pain or jaundice) or increases in bilirubin ≥ 2 x ULN, treatment must be stopped. There is no experience with the reintroduction of bosentan in these circumstances.

In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with bosentan in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with bosentan (see information about patients who develop hepatic abnormalities during treatment under DOSAGE AND ADMINISTRATION). The contribution of bosentan in these cases could not be excluded.

<u>Hepatic Impairment</u>
Bosentan is contraindicated in patients with moderate or severe hepatic impairment (see PHARMACOLOGY, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION). In addition, bosentan should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because these patients are at a greater risk and monitoring liver injury may be more difficult. Patients with mild hepatic impairment (hepatic aminotransferases 1 to 3 x ULN) may be commenced on bosentan, but have an increased risk of hepatotoxicity (see ADVERSE REACTIONS).

Haematological Changes
Treatment with bosentan caused a dose-related decrease in haemoglobin and haematocrit. 10% of 693 bosentan patients had clinically significant reductions in haematocrit or haemoglobin, with decreases in erythrocytes, and 5% had anaemia. Haemoglobin levels should be monitored periodically. It is recommended that haemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in haemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

A decrease in haemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose haemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment. Most of this decrease of haemoglobin concentration was detected during the first few weeks of bosentan treatment and haemoglobin levels stabilised by 4-12 weeks of bosentan treatment.

In placebo-controlled studies of all uses of bosentan, marked decreases in haemoglobin (> 15% decrease from baseline resulting in values < 1 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. 3% of bosentan patients had serious anaemia requiring withdrawal from the studies and/or blood transfusion. In patients with PAH treated with doses of 125 mg and 250 mg twice daily, marked decreases in haemoglobin occurred in 3% compared to 1% in placebo-treated patients. Stopping bosentan generally resulted in patients' haemoglobin or haematocrit returning to baseline levels quickly.

During the course of treatment the haemoglobin concentration remained within normal limits in 68% of bosentan treated patients compared to 76% of placebo patients.

The explanation for the change in haemoglobin is not known, but it does not appear to be haemorrhage or haemolysis.

In the post-marketing period, cases of anaemia requiring red blood cell transfusion have been reported.

Pulmonary Veno-occlusive Disease
Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema occur when bosentan is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered. In the post-marketing period there have been rare reports of pulmonary oedema in patients treated with bosentan who had a suspected diagnosis of pulmonary veno-occlusive disease.

PAH Patients with Concomitant Left Ventricular Failure
No specific study has been performed in patients with pulmonary hypertension and concomitant left ventricular dysfunction. However, 1611 patients (804 bosentan- and 807 placebo-treated patients with severe chronic heart failure (CHF) were treated for a

mean duration of 1.5 years in a placebo-controlled study. In this study there was an increased incidence of hospitalisation due to CHF during the first 4-8 weeks of treatment with bosentan, which could have been the result of fluid retention. In this study, fluid retention was manifested by early weight gain, decreased haemoglobin concentration and increased incidence of leg oedema. At the end of this study, there was no difference in overall hospitalisation for heart failure nor in mortality between bosentan- and placebo-treated patients. Consequently, it is recommended that patients be monitored for signs of fluid retention (e.g. weight gain), especially if they concomitantly suffer from severe systolic dysfunction. Should this occur, starting treatment with diuretics is recommended, or the dose of existing diuretics should be increased.

Treatment with diuretics should be considered in patients with evidence of fluid retention before the start of treatment with bosentan.

Use in Patients with Pre-existing Anaemia
Particular caution should be exercised when initiating bosentan in patients with haemoglobin or haematocrit more than 30% below the lower limit of normal. Such patients were excluded from clinical trials of bosentan. The cause of anaemia should be determined and managed as appropriate, and haematological parameters should be checked more frequently than usual.

Use in Patients with Pre-existing Hypotension
Particular caution should be exercised when initiating bosentan in patients with pre-existing hypotension, and blood pressure in such patients should be monitored closely. Patients with systolic blood pressure < 85 mmHg were excluded from clinical trials of bosentan.

Use in Patients receiving Epoprostenol
In a randomised, double blind trial (BREATHE-2), 32 patients were commenced on epoprostenol, to which bosentan (n=22) or placebo (n=11) was added two days later. The treatments were then carried out for 16 weeks. The trial failed to show any significant clinical benefit (6 minute walk, dyspnoea score, WHO functional class) or pharmacodynamic effect. The co-administration of bosentan with epoprostenol is, therefore, not recommended.

Use in CHD Patients
In the BREATHE-5 trial, oxygen saturation did not deteriorate in patients treated with bosentan compared with placebo. However, it is recommended as standard medical care that CHD patients have their oxygen saturation monitored as clinically indicated.

Use in Patients with HIV Infection
If treatment with bosentan is initiated in patients who require ritonavir-boosted protease inhibitors, the patient's tolerability of bosentan should be closely monitored with special attention, at the beginning of the initiation phase, to the risk of hypotension and to liver function tests. An increased long-term risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. Due to the potential for interactions related to the inducing effect of bosentan on CYP450 (see

INTERACTIONS WITH OTHER MEDICINES), which could affect the efficacy of antiretroviral therapy, these patients should also be monitored carefully regarding their HIV infection.

Effects on Fertility

Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear irreversible.

In fertility studies in which male and female rats were treated with bosentan at oral doses of up to 1,500 mg/kg/day (50 times the MRHD on a mg/m^2 basis) or intravenous doses of up to 40 mg/kg/day, no effects on sperm count, sperm motility, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest dose tested) for two years but not at doses as high as 1,500 mg/kg/day (about 50 times the MRHD) for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4,500 mg/kg/day (about 75 times the MRHD), or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 30 times the MRHD).

Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were treated with bosentan 62.5 mg bid for 4 weeks followed by 125 mg bid for 5 months to assess any effects on testicular function. Twenty three completed the study and 2 discontinued due to adverse events not related to testicular function. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after two months the sperm count had returned to baseline levels. The relevance of this observation is uncertain considering the large natural intrasubject variability of sperm counts. Although, based on this finding, it cannot be excluded that endothelin receptor antagonists such as bosentan may have an effect on spermatogenesis, the absence of a systematic effect of chronic bosentan treatment on testicular function in humans observed in this study is in line with the toxicology data for bosentan.

Use in Pregnancy (Category X)

Bosentan was teratogenic in rats given oral doses ≥ 60 mg/kg/day (twice the maximum recommended human oral therapeutic dose of 125 mg twice daily, on a mg/m^2 basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 mg and 300 mg/kg/day (2 and 10 times, respectively, the maximum recommended human dose on a mg/mg^2 basis). Although birth defects were not observed in rabbits given oral doses of up to 1,500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations

induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

There are minimal data on the use of bosentan in pregnant women from very few cases received in the post-marketing period. The potential risk for humans is still unknown, but bosentan must be considered a human teratogen and must not be used during pregnancy. Women must not become pregnant for at least 3 months after stopping treatment with bosentan. Bosentan is contraindicated in pregnancy (see CONTRAINDICATIONS)

Use in lactation
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking bosentan is not recommended.

Paediatric use
Various doses of bosentan have been assessed in a clinical study in paediatric patients with PPH or PAH related to congenital systemic to pulmonary communications, either as monotherapy or combined with epoprostenol (see CLINICAL TRIALS). The results indicate that the doses used were effective and appropriate in terms of safety and pharmacokinetics (see DOSAGE AND ADMINISTRATION - Dosage Adjustment in Children).

Use in the Elderly
Clinical studies of bosentan were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects; greater sensitivity to bosentan cannot be ruled out. Conditions more common in the elderly, such as hepatic impairment, renal impairment and decreased cardiac function, as well as concomitant diseases and other drug therapy, can have clinically significant effects on bosentan pharmacokinetics (see PHARMACOLOGY - Pharmacokinetics). Caution should be exercised in treating elderly patients, and close clinical monitoring is required. The lowest effective dose should be used to prevent the occurrence of side effects (see DOSAGE AND ADMINISTRATION).

Genotoxicity
There was no evidence for mutagenic or clastogenic activity of bosentan in a standard battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenisis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay.

Carcinogenicity
Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and combined adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 12 mg twice daily on a mg/ m^2 basis). In the same study, doses greater than 2,000 mg/kg/day (about 32 times the [MRHD]) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16

times the [MRHD]; no effect dose of 125 mg/kg/day, about 4 times the MRHD) and females at doses of 3,000 mg/kg/day (no-effect dose of 2,000 mg/kg/day, about 128 times the MRHD). An increased incidence of thyroid follicular adenomas was also observed in male rats at doses as low as 2,000 mg/kg/day (about 32 times the MRHD). However, the relevance of these findings to humans is not known.

Driving/Operating Machinery

No studies on the effect of bosentan on the ability to drive and use machines have been performed. Bosentan may induce hypotension, with symptoms of dizziness, blurred vision or syncope that could affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Other Medicines that Affect Bosentan

Demonstrated Interactions

Co-administration of bosentan 125 mg twice daily for 6 days and ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to bosentan 83%. No dose adjustment of bosentan is considered necessary, however, due to the possibility of increased exposure to bosentan, more frequent liver function monitoring is recommended during concomitant ketoconazole use.

Co-administration of bosentan and cyclosporine A is contraindicated. When co-administered, initial trough concentrations of bosentan were approximately 30-fold higher than those measured after bosentan alone. At steady state, bosentan plasma concentrations were 3- to 4-fold higher than with bosentan alone.

Co-administration of bosentan and glibenclamide is contraindicated. Concomitant, steady state administration of bosentan 125 mg twice daily and glibenclamide decreased bosentan concentrations 30%. Concomitant glibenclamide administration predisposed patients to an increased risk of elevated liver aminotransferases.

Rifampicin

Co-administration of bosentan and rifampicin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose. Co-administration in 9 healthy subjects of bosentan 125 mg twice daily for 7 days and rifampicin, a potent inducer of CYP2C9 and CYP3A4, decreased the plasma concentrations of bosentan by 58%, and this decrease could achieve almost 90% in an individual case. The effect of bosentan on rifampicin levels has not been assessed. A subsequent significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure liver function tests (LFTs) weekly for the first 4 weeks before reverting to normal monitoring. Data on other CYP3A4 inducers, e.g. carbamazepine, phenobarbital, phenytoin and St John's Wort are lacking, but their concomitant administration is expected to lead to reduced systemic exposure to bosentan. A clinically significant reduction of efficacy cannot be excluded.

Co-administration of bosentan 125 mg twice daily and lopinavir+ritonavir 400+100 mg twice daily during 9.5 days in healthy volunteers, resulted in initial trough plasma

concentrations of bosentan that were approximately 48-fold higher than those measured after bosentan administered alone. On day 9, plasma concentrations of bosentan were approximately 5-fold higher than with bosentan administered alone. Inhibition by ritonavir of transport protein mediated uptake into hepatocytes and of CYP3A4, thereby reducing the clearance of bosentan, most likely causes this interaction. If administered concomitantly with lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, the patient's tolerability of bosentan should be monitored. In particular, markers of liver dysfunction such as LFTs and vascular (hypotension) adverse events should be monitored. After co-administration of bosentan for 9.5 days, the plasma exposures of lopinavir and ritonavir decreased to a clinically non-significant extent (by approximately 14% and 17%, respectively). However, full induction by bosentan might not have been reached and a further decrease of protease inhibitors cannot be excluded. Appropriate monitoring of HIV therapy and indices of HIV infection progression are also recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors (refer to PRECAUTIONS section).

Other antiretroviral agents
No specific recommendation can be made with regard to other available antiretroviral agents due to the lack of data. It is emphasised that due to the marked hepatotoxicity of nevirapine, which could accumulate with bosentan liver toxicity, this combination is not recommended.

Losartan, digoxin and simvastatin did not affect bosentan plasma levels.

Theoretical Interactions
Concomitant administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole and ritonavir) and a CYP2C9 inhibitor (such as voriconazole) in combination with bosentan may result in increased plasma levels of bosentan.

Caution should be exercised when bosentan is co-administered with known hepatotoxic drugs.

Concomitant use of bosentan with fluconazole is not recommended. Although not studied, this combination may lead to large increases in plasma concentrations of bosentan.

Other Interactions Investigated
Digoxin, phenytoin and tolbutamide may cause a slight increase in free bosentan, but this slight increase is unlikely to be of clinical importance. There was no indication of a serum protein binding interaction between warfarin and bosentan.

Concomitant administration of bosentan and epoprostenol has shown to be safe and efficacious in a clinical study with paediatric PPH/PAH patients. The pharmacokinetics were similar to those in adult patients and healthy subjects in other studies.

Co-administration of tacrolimus or sirolimus and bosentan has not been studied in man but may result in increased plasma concentrations of bosentan in analogy to co-

administration with cyclosporine A. Concomitant bosentan may reduce the plasma concentrations of tacrolimus and sirolimus. Therefore, concomitant use of bosentan and tacrolimus or sirolimus is not advisable. Patients in need of the combination should be closely monitored for adverse events related to bosentan and for tacrolimus and sirolimus blood concentrations.

Effects of Bosentan on Other Medicines

Demonstrated Interactions

Co-administration of bosentan and glibenclamide is contraindicated. Concomitant, steady state administration of bosentan 125 mg twice daily and glibenclamide decreased glibenclamide concentrations 40%. Concomitant glibenclamide administration predisposed patients to an increased risk of elevated liver aminotransferases.

Co-administration of bosentan 500 mg twice daily for 6 days decreased the plasma concentrations of S-and R-warfarin by 29% and 38%, respectively. Clinical experience of concomitant administration of bosentan with warfarin in patients with PAH did not result in clinically relevant changes in International Normalised Ratio (INR) or warfarin dose (baseline versus end of the clinical studies). In addition, the frequency of changes in warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. No dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated but intensified monitoring of INR is recommended, especially during the bosentan initiation and the up-titration period.

Co-administration of bosentan 500 mg twice daily for 7 days decreased the AUC, C_{max} and C_{min} of digoxin by 12%, 9% and 23%, respectively. Higher doses of digoxin may be required.

Co-administration of bosentan 125 mg twice daily for 5 days decreased the plasma concentrations of simvastatin, and its active b-hydroxy acid metabolite by 49% and 60%, respectively. Monitoring of cholesterol levels and subsequent dosage adjustment should be considered.

Co-administration of bosentan and cyclosporine A is contraindicated. Concomitant, steady state administration of bosentan 500 mg twice daily and cyclosporine A decreased cyclosporine A concentrations 50%.

Single dose bosentan did not affect nimodipine plasma levels.

Co-administration of bosentan 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease of the sildenafil AUC and a 50% increase of the bosentan AUC. Caution is recommended in case of co-administration. The reduction in sildenafil plasma concentration with co-administration of bosentan has also been reported in a study of patients with primary arterial hypertension.

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БОГОЛЕПОВ А.А.

Hormonal contraceptives, including oral, injectable, transdermal and implantable contraceptives
An interaction study demonstrated that co-administration of bosentan and the oral hormonal contraceptive Ortho-Novum produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, hormonal contraceptives, including oral, injectable transdermal and implantable forms may not be reliable when bosentan is co-administered. Women should practise additional methods of contraception and not rely on hormonal contraception alone when taking bosentan.

Theoretical Interactions
Bosentan is an inducer of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4. *In vitro* data also suggest an induction of CYP2C19. Consequently, plasma concentrations of drugs metabolised by these isoenzymes will be decreased when bosentan is co-administered. The possibility of altered efficacy of medicinal products metabolised by these isoenzymes should be considered. The dosage of these products may need to be adjusted after initiation, dose change or discontinuation of concomitant bosentan treatment. Specifically, bosentan is expected to reduce the exposure to statins and oral hypoglycaemic agents that are predominantly metabolised by CYP3A4 or CYP2C9.

Bosentan is metabolised by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been studied. The combination should be used with caution. Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole and ritonavir) and a CYP2C9 inhibitor (such as voriconazole) with bosentan is not recommended.

Nimodipine concentrations could decrease after multiple-dose administration of bosentan.

Other Interactions Investigated
Bosentan did not lead to any significant changes in the serum protein binding of digoxin, glibenclamide, phenytoin, or warfarin. However, bosentan slightly increased the free serum concentrations of tolbutamide, but this slight increase is unlikely to be of clinical importance.

In vitro data demonstrated that bosentan had no relevant inhibitory effect on the CYP isoenzymes tested (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4). Consequently, bosentan is not expected to increase the plasma concentrations of medicinal products metabolised by these isoenzymes.

ADVERSE EFFECTS

In 20 placebo-controlled studies, conducted in a variety of therapeutic indications, a total of 2,486 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 1,838 patients were treated with placebo. The mean treatment duration was 45 weeks. In 5 controlled clinical studies in patients with PAH 317 patients were treated with bosentan at daily doses ranging from 125 to 500 mg and 200 patients were treated with placebo. The mean treatment duration was 21 weeks.

The most commonly reported adverse events (occurring in at least 1% of patients on bosentan and more frequently than on placebo) were headache (11.1% vs 9.4%), upper respiratory tract infection (10.6% vs 9.0%), oedema peripheral (9.7% vs 8.3%), anaemia (6.2% vs 3.0%), haemoglobin decreased (3.7% vs 1.6%), alanine aminotransferase increased (3.3% vs 0.9%), flushing (3.2% vs 1.3%) and liver function test abnormal (3.1% vs 1.0%), see Table 5.

Table 5: Adverse Events in 20 placebo-controlled studies

	Placebo		Bosentan		Difference from placebo
	N=1838		N=2486		
Preferred Term	**n**	**%**	**n**	**%**	
Headache	172	9.4%	275	11.1%	1.7%
Upper respiratory tract infection	166	9.0%	264	10.6%	1.6%
Oedema peripheral	153	8.3%	242	9.7%	1.4%
Nasopharyngitis	107	5.8%	154	6.2%	0.4%
Anaemia	56	3.0%	153	6.2%	3.1%
Idiopathic pulmonary fibrosis*	97	5.3%	145	5.8%	0.6%
Sinusitis	59	3.2%	91	3.7%	0.5%
Haemoglobin decreased	29	1.6%	91	3.7%	2.1%
Alanine aminotransferase increased	17	0.9%	82	3.3%	2.4%
Lower respiratory tract infection	56	3.0%	81	3.3%	0.2%
Flushing	23	1.3%	79	3.2%	1.9%
Liver function test abnormal	18	1.0%	77	3.1%	2.1%
Aspartate aminotransferase increased	19	1.0%	68	2.7%	1.7%
Pyrexia	37	2.0%	57	2.3%	0.3%
Pruritus	34	1.8%	57	2.3%	0.4%
Hepatic enzyme increased	13	0.7%	56	2.3%	1.5%
Gastrooesophageal reflux disease	23	1.3%	51	2.1%	0.8%
Epistaxis	30	1.6%	46	1.9%	0.2%
Nasal congestion	22	1.2%	43	1.7%	0.5%
Oedema	19	1.0%	43	1.7%	0.7%
Angina unstable	26	1.4%	40	1.6%	0.2%
Oropharyngeal pain	24	1.3%	37	1.5%	0.2%
Vision blurred	24	1.3%	36	1.4%	0.1%
Rhinitis	16	0.9%	33	1.3%	0.5%
Haematocrit decreased	9	0.5%	32	1.3%	0.8%
Vertigo	18	1.0%	30	1.2%	0.2%
Orthostatic hypotension	16	0.9%	29	1.2%	0.3%
Influenza like illness	16	0.9%	25	1.0%	0.1%
Joint swelling	11	0.6%	25	1.0%	0.4%
Sinus congestion	9	0.5%	25	1.0%	0.5%

*Events of idiopathic pulmonary fibrosis (IPF) referred to progression of the underlying disease in studies conducted in IPF patients

Additional adverse events occurring in the subset of patients treated for PAH, in at least 3% of patients on bosentan and more frequently than on placebo are presented in Table 6.

Table 6: Additional adverse events in 5 placebo-controlled studies in PAH

Preferred Term	Placebo N=200		Bosentan N=317		Difference from placebo
	n	%	n	%	
Diarrhoea	16	8.0%	27	8.5%	0.5%
Chest pain	9	4.5%	16	5.0%	0.5%
Palpitations	3	1.5%	14	4.4%	2.9%
Syncope	8	4.0%	13	4.1%	0.1%
Arthralgia	3	1.5%	11	3.5%	2.0%
Hypotension	6	3.0%	10	3.2%	0.2%
Hot flush	2	1.0%	10	3.2%	2.2%

Treatment with bosentan has been associated with dose-dependent elevations in liver aminotransferases and decreases in haemoglobin concentration (see PRECAUTIONS).

Laboratory Abnormalities
Increased liver aminotransferases, and decreased haemoglobin and haematocrit (see PRECAUTIONS).

In the post-marketing period cases of anaemia requiring red blood cell transfusion have been reported.

Post-marketing Experience
Based on an exposure of about 121,000 patients to bosentan in the post-marketing period, the majority of adverse events have been similar to those reported in clinical trials.

The following additional adverse reactions in Table 7 have been reported in the post marketing use. The reactions are ranked under headings of frequency using the following convention common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000).

Table 7: Post-marketing Adverse Events

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Not known[1]	Anaemia or haemoglobin decreases requiring red blood cell transfusion
	Uncommon	Thrombocytopenia
	Uncommon	Neutropenia, leukopenia
Immune system disorders	Common	Hypersensitivity reactions (including dermatitis, pruritus and rash)
	Rare	Anaphylaxis and/or angioedema
Hepatobiliary disorders	Uncommon	Aminotransferase elevations associated with hepatitis and/or jaundice

БОГОЛЕПОВ А.А.

System organ class	Frequency	Adverse reaction
	Rare	Liver cirrhosis, liver failure
Eye disorders	Not known[1]	Blurred vision

1 Frequency cannot be estimated from the available data.

In the post-marketing period rare cases of unexplained hepatic cirrhosis were reported after prolonged therapy with bosentan in patients with multiple comorbidities and drug therapies. There have also been rare reports of liver failure. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with bosentan.

DOSAGE AND ADMINISTRATION

Bosentan should be administered under the supervision of a physician experienced in the management of PAH. Bosentan treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks. Efficacy was demonstrated in clinical trial subjects who increased to a maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.

Tablets should be administered morning and evening with or without food.
Serum liver aminotransferase (AST & ALT) levels must be measured prior to initiation of treatment with bosentan and monthly thereafter for the duration of treatment (see PRECAUTIONS - Potential Liver Injury). If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated, as detailed below.

Dosage in Patients with Hepatic Impairment

Patients with Hepatic Abnormalities before Starting BOSENTAN Treatment

Bosentan must not be initiated in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C) (see CONTRAINDICATIONS).

Bosentan may be initiated at the usual starting dose in patients with mild hepatic impairment (Child-Pugh Class A, hepatic aminotransferases n< 3 x ULN). However, the use of bosentan in these patients may be associated with an increased risk of hepatotoxicity (see ADVERSE EFFECTS).

Patients who Develop Hepatic Abnormalities during Treatment

In patients who develop hepatic abnormalities during treatment with bosentan, the following actions should be taken:

Aminotransferase Abnormalities

ALT/AST levels: Treatment and Monitoring Recommendations

> 3 and ≤ 5 x ULN

Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).

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> 5 and ≤ 8 x ULN
Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider reintroduction of the treatment (see below).

> 8 x ULN
Treatment should be stopped and re-introduction of bosentan should not be considered. There is no experience with the re-introduction of bosentan in these circumstances.

If bosentan is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

Bilirubin Abnormalities
If liver aminotransferase elevations are accompanied by increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the reintroduction of bosentan in these circumstances.

Clinical Symptoms or Signs of Liver Injury
If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue), treatment must be stopped. There is no experience with the re-introduction of bosentan in these circumstances.

Use in Women of Childbearing Potential
Bosentan treatment should only be initiated in women of childbearing potential following a negative pregnancy test and only in those who practice reliable contraception that does not depend solely upon hormonal contraceptives including oral, injectable, transdermal or implantable contraceptives. Double barrier contraception is recommended. Repeated monthly pregnancy tests during treatment with bosentan are recommended (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES - Hormonal contraceptives including oral, injectable, transdermal and implantable contraceptives). Women must not become pregnant for at least three months after stopping treatment with bosentan.

Dosage in Renally Impaired Patients
The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment. In patients with severe renal impairment (creatinine clearance 15-30 mL/min), plasma concentrations of bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2-fold compared to people with normal renal function. These differences do not appear to be clinically important (see PHARMACOLOGY - Pharmacokinetics, Special Populations - Renal Impairment).

Dosage in Geriatric Patients
Clinical studies of bosentan were not adequate to determine whether subjects aged 65 and older respond differently than younger subjects; greater sensitivity to bosentan cannot be ruled out. Conditions more common in the elderly, such as hepatic

impairment, renal impairment and decreased cardiac function, as well as concomitant diseases and other drug therapy, can have a clinically significant effect on bosentan pharmacokinetics (see PHARMACOLOGY - Pharmacokinetics and PRECAUTIONS). Caution should be exercised in dose selection for elderly patients, and close clinical monitoring is required. The lowest effective dose should be used to prevent the occurrence of side effects (see DOSAGE and ADMINISTRATION).

Dosage Adjustment in Children

There is limited experience with the use of bosentan in children based on a pharmacokinetic study conducted in 19 children with PAH (see PHARMACOLOGY - Pharmacokinetics and CLINICAL TRIALS). The pharmacokinetic findings showed that systemic exposure in children with PAH was lower than in adults with PAH. Although the number of patients studied in each dose group was generally insufficient to establish the optimal dosing regimen, the following doses are recommended in children aged 3 years and over:

	Starting dose (First 4 weeks)	Maintenance dose (Week 5 onwards)
Body weight 10 to 20 kg	31.25 mg ONCE daily	31.25 mg twice daily
Body weight > 20 to 40 kg	31.25 mg twice daily	62.5 mg twice daily
Body weight > 40 kg	62.5 mg twice daily	125 mg twice daily

Dosage Adjustment in Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg twice daily.

Discontinuation of Treatment

There is limited experience with abrupt discontinuation of bosentan. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered. Intensified monitoring is recommended during the discontinuation period.

OVERDOSAGE

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

Bosentan has been given as a single dose of up to 2,400 mg in normal volunteers, or up to 2,000 mg/day for 2 months in patients, without any major clinical consequences.

The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 mg and 1,000 mg twice daily of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but not serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed.

Massive overdosage may result in pronounced hypotension requiring active cardiovascular support. In the post-marketing period there was one reported overdose of 10,000 mg of bosentan taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating and blurred vision. He recovered completely within 24 hours with blood pressure support. Note: bosentan is not removed through dialysis.

PRESENTATION AND STORAGE CONDITIONS

BOSENTAN SANDOZ 125 mg film tablet is a light orange colour, oval, biconvex film tablet. Each tablet contains 129.082mg bosentan (as monohydrate) active substance, equivalent to 125mg bosentan, packaged in blister packs in pack sizes of 60 tablets per pack.

BOSENTAN SANDOZ 62.5 mg film tablet is a light orange colour, round, biconvex Film Coated Tablet. Each tablet contains 64.541 mg bosentan (as monohydrate) active substance, equivalent to 62.5 mg bosentan, packaged in blister packs in packs of 60 tablets per pack.

Not all presentations may be marketed in Australia.

Store below 25 °C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 726 369

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

22/11/2016

БОГОЛЕПОВ А.А.

DATE OF MOST RECENT AMENDMENT
20/11/2017

До реєстраційного посвідчення

№_____

від _____

Переклад українською мовою, автентичність якого підтверджена Заявником або його уповноваженою особою, інструкції про застосування лікарського засобу або інформації про застосування лікарського засобу, затвердженої відповідно до нормативних вимог країни Заявника/Виробника або країни, регуляторний орган якої керується високими стандартами якості, що відповідають стандартам, рекомендованим ВООЗ, та/або згідно з результатами клінічних випробувань, засвідчений підписом уповноваженої особи, що виступає від імені Заявника

БОГОЛЕПОВ А.А.

SANDOZ Nardo Alessia Aceto Sarah Jane
stylegraph C. 02310/7
Istruzione | Bosentan Sandoz compresse rivestite con film | 180 x 590 | VENDITA | ITALIA | 11/04/18
1 | NERO
1803-03 | A20013069/02 | 10428 | 8,5
IMPIANTI DI PROPRIETÀ DI SANDOZ S.p.A. VIETATO L'UTILIZZO NON AUTORIZZATO E LA MANOMISSIONE

APPROVED
By Oktay ÖZ at 8:07 pm, Apr 20, 2018

Foglio illustrativo: informazioni per l'utilizzatore

Bosentan Sandoz 62,5 mg compresse rivestite con film
Bosentan Sandoz 125 mg compresse rivestite con film

SANDOZ A Novartis Division

Medicinale equivalente

Legga attentamente questo foglio prima di prendere questo medicinale perché contiene importanti informazioni per lei.
- Conservi questo foglio. Potrebbe aver bisogno di leggerlo di nuovo.
- Se ha qualsiasi dubbio, si rivolga al medico o al farmacista.
- Questo medicinale è stato prescritto soltanto per lei. Non lo dia ad altre persone, anche se i sintomi della malattia sono uguali ai suoi, perché potrebbe essere pericoloso.
- Se si manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio, si rivolga al medico o al farmacista. Vedere paragrafo 4.

Contenuto di questo foglio:

1. Che cos'è Bosentan Sandoz e a cosa serve

Le compresse di Bosentan Sandoz contengono bosentan che blocca un ormone presente naturalmente nell'organismo chiamato endotelina-1 (ET-1), che causa un restringimento dei vasi sanguigni. Bosentan Sandoz comporta, quindi, una dilatazione dei vasi ed appartiene alla classe di medicinali denominati "antagonisti del recettore dell'endotelina".

Bosentan Sandoz è usato per trattare:
- **Ipertensione arteriosa polmonare** (PAH): la PAH è una malattia caratterizzata da un grave restringimento dei vasi sanguigni dei polmoni con conseguente aumento di pressione nei vasi sanguigni che portano il sangue dal cuore ai polmoni (arterie polmonari). Questa pressione riduce la quantità di ossigeno che può passare nel sangue attraverso i polmoni, rendendo l'attività fisica più difficoltosa. Bosentan Sandoz allarga le arterie polmonari, facilitando il pompaggio del sangue al loro interno da parte del cuore; ciò determina una riduzione della pressione sanguigna ed un'attenuazione dei sintomi.

  Bosentan Sandoz è usato per trattare pazienti affetti da ipertensione arteriosa polmonare (PAH) di classe III, per migliorare la capacità di esercizio (possibilità di svolgere attività fisica) ed i sintomi. La "classe" riflette la gravità della malattia: "classe III" comporta una marcata limitazione all'attività fisica. Alcuni miglioramenti sono stati evidenziati anche in pazienti con PAH di classe II. "Classe II" comporta delle minori limitazioni nell'attività fisica. La PAH per la quale Bosentan Sandoz è indicato può essere:
  - primaria (senza una causa identificabile o familiare);
  - causata dalla sclerodermia (definita anche sclerosi sistemica, una malattia caratterizzata da un anormale crescita del tessuto connettivo che sostiene la cute ed altri organi);
  - causata da difetti congeniti (innati) del cuore con shunt (vie di passaggio anormali) che determinano un flusso anormale di sangue attraverso il cuore ed i polmoni.
- **Ulcere digitali:** (lesione delle dita di mani e piedi) in pazienti adulti con una condizione chiamata sclerodermia. Bosentan Sandoz riduce il numero delle nuove ulcere delle dita di mani e piedi.

2. Cosa deve sapere prima di prendere Bosentan Sandoz

Non prenda Bosentan Sandoz
- **se è allergico a bosentan** o ad una qualsiasi degli altri componenti di questo medicinale (elencati al paragrafo 6)
- **se ha disturbi al fegato** (chieda al medico)
- **se è in gravidanza o può dare inizio ad una gravidanza** poiché non usa metodi anticoncezionali affidabili. Per favore legga le informazioni riportate in "Contraccettivi" e in "Altri medicinali e Bosentan Sandoz"
- **se è in trattamento con ciclosporina A** (un medicinale usato dopo un trapianto d'organo o per il trattamento della psoriasi)

Si rivolga al medico se una delle situazioni descritte sopra la riguarda.

Avvertenze e precauzioni

Si rivolga al medico o al farmacista prima di prendere Bosentan Sandoz.

Esami che saranno prescritti dal medico prima del trattamento
- un esame del sangue per verificare la sua funzionalità epatica
- un esame del sangue per controllare la presenza di anemia (emoglobina bassa)
- un test di gravidanza se lei è una donna in età fertile

In alcuni pazienti in terapia con Bosentan Sandoz sono stati riscontrati esiti anomali negli esami per la funzionalità epatica ed anemia (emoglobina bassa).

Esami che saranno prescritti dal medico durante il trattamento
Durante il trattamento con Bosentan Sandoz il medico le prescriverà regolarmente esami del sangue, in modo tale da monitorare eventuali cambiamenti della funzione del fegato e dei livelli di emoglobina.

Per tutti questi esami fare riferimento anche alla Carta Informativa del Paziente (contenuta nella confezione di Bosentan Sandoz). È importante che lei si sottoponga a questi esami del sangue ad intervalli regolari durante l'intero periodo di assunzione di Bosentan Sandoz. Si consiglia di annotare sulla Carta Informativa del Paziente la data dell'esame più recente e anche quella del prossimo esame previsto (chiedere la data al medico), questo l'aiuterà a ricordare quando deve fare l'esame successivo.

Esami del sangue per la funzione del fegato
Verranno effettuati ogni mese per tutta la durata del trattamento con Bosentan Sandoz. In seguito ad incremento della dose verrà effettuato un esame addizionale dopo 2 settimane.

Esami del sangue per l'anemia
Verranno effettuati ogni mese per i primi 4 mesi del trattamento e successivamente ogni 3 mesi, in quanto i pazienti che assumono Bosentan Sandoz possono sviluppare anemia.

Se questi risultati sono anomali, il medico può decidere di ridurre la dose o sospendere il trattamento con Bosentan Sandoz ed effettuare ulteriori esami per determinarne la causa.

Bambini e adolescenti

Bosentan Sandoz non è raccomandato nei pazienti pediatrici con sclerosi sistemica ed ulcere digitali attive. Bosentan Sandoz non deve essere usato anche nei bambini con peso corporeo inferiore a 31 kg affetti da ipertensione arteriosa polmonare. Vedere anche il paragrafo 3. Come prendere Bosentan Sandoz.

Altri medicinali e Bosentan Sandoz
Informi il medico o il farmacista se sta assumendo, ha recentemente assunto o potrebbe assumere qualsiasi altro medicinale, inclusi i medicinali ottenuti senza prescrizione medica.
È importante, soprattutto, informare il medico se sta prendendo:
- ciclosporina A (un medicinale utilizzato dopo i trapianti e per il trattamento della psoriasi) che non deve essere usata insieme a Bosentan Sandoz
- sirolimus o tacrolimus, che sono medicinali usati dopo trapianti, il cui uso insieme a Bosentan Sandoz non è raccomandato
- glibenclamide (un medicinale per il diabete), rifampicina (un medicinale per la tubercolosi), fluconazolo e ketoconazolo (medicinali per il trattamento di infezioni da funghi), nevirapina (un medicinale per l'HIV), in quanto l'uso di questi medicinali insieme a Bosentan Sandoz non è raccomandato
- altri medicinali per il trattamento dell'infezione da HIV che possono richiedere un monitoraggio speciale se utilizzati insieme al Bosentan Sandoz
- contraccettivi ormonali, che non sono efficaci come unico metodo di contraccezione quando assume Bosentan Sandoz. All'interno della confezione di Bosentan Sandoz troverà una Carta Informativa del Paziente che dovrà leggere attentamente. Il medico e/o il ginecologo stabilirà il metodo contraccettivo appropriato per lei.
- altri medicinali per il trattamento dell'ipertensione polmonare: sildenafil e tadalafil
- warfarin (un agente anticoagulante)
- simvastatina (usata per trattare l'ipercolesterolemia)

Bosentan Sandoz con cibi e bevande
Bosentan Sandoz può essere preso a digiuno o a stomaco pieno.

Gravidanza, allattamento e fertilità
Se è in corso una gravidanza, se sospetto o sta pianificando una gravidanza, o se sta allattando con latte materno, chieda consiglio al medico o al farmacista prima di prendere questo medicinale.

Donne in età fertile
NON assuma Bosentan Sandoz se lei è in stato di gravidanza o sta cercando di rimanere incinta.

Test di gravidanza
Bosentan Sandoz può nuocere al nascituro concepito prima o durante il trattamento. Se lei è una donna in età fertile, il medico le chiederà di effettuare un test di gravidanza prima di iniziare l'assunzione di Bosentan Sandoz e di effettuarlo, quindi, regolarmente durante il trattamento con Bosentan Sandoz.

Contraccettivi
Se lei è una donna in età fertile, utilizzi un metodo affidabile di controllo delle nascite (contraccettivo) mentre prende Bosentan Sandoz. Il medico o ginecologo la consiglierà sui metodi contraccettivi affidabili durante il trattamento con Bosentan Sandoz. Poiché Bosentan Sandoz può rendere inefficace la contraccezione ormonale (ad esempio contraccettivi orali, iniettabili, impiantabili o cerotti cutanei), questo metodo da solo non è affidabile. Quindi, se lei usa contraccettivi ormonali deve usare anche un metodo di barriera (es. profilattico femminile, diaframma, spugna contraccettiva) oppure anche il suo partner deve utilizzare il profilattico). All'interno della confezione di Bosentan Sandoz troverà una Carta Informativa del Paziente. Lei dovrà compilare questa carta e portarla al suo medico alla prossima visita, in questo modo il medico o il ginecologo potranno valutare se lei ha bisogno di metodi contraccettivi addizionali o alternativi affidabili. Si raccomanda di effettuare un test di gravidanza ogni mese durante il trattamento con Bosentan Sandoz se lei è in età fertile.

Informi immediatamente il medico se inizia una gravidanza durante il trattamento con Bosentan Sandoz o se ha intenzione di dare inizio ad una gravidanza nell'immediato futuro.

Allattamento
Informi immediatamente il **medico se sta allattando**. Si consiglia di interrompere l'allattamento al seno in caso le venga prescritta Bosentan Sandoz in quanto non si sa se questo medicinale viene escreto nel latte materno.

Fertilità
Se lei è un uomo che assume Bosentan Sandoz è possibile che questo medicinale riduca la conta degli spermatozoi. Non si può escludere che questo possa compromettere la possibilità di concepire un figlio. Parli con il medico se ha domande su questo argomento.

Guida di veicoli e utilizzo di macchinari
Bosentan Sandoz può indurre ipotensione (riduzione della sua pressione sanguigna) che può provocarle capogiri, influenzare la sua vista e la sua capacità di guidare veicoli e usare macchinari. Pertanto se lei avverte un senso di vertigine o ha offuscamento della vista durante il trattamento con Bosentan Sandoz, non guidi o non utilizzi strumenti o macchinari di alcun genere.

3. Come prendere Bosentan Sandoz

Prenda questo medicinale seguendo sempre esattamente le istruzioni del medico o del farmacista. Se ha dubbi consulti il medico o il farmacista.

Il trattamento con Bosentan Sandoz deve essere iniziato e monitorato solo da un medico che ha esperienza nel trattamento della PAH o della sclerosi sistemica.

Dose raccomandata

Adulti
Negli adulti il trattamento ha inizio normalmente con l'assunzione di una compressa da 62,5 mg due volte al giorno (mattina e sera) per le prime 4 settimane, in seguito il medico consiglierà soltanto di assumere una compressa da 125 mg due volte al giorno a seconda della risposta a Bosentan Sandoz riscontrata.

Bambini ed adolescenti
La dose raccomandata nei bambini è solo per la PAH. Per bambini di età uguale o maggiore a 1 anno il trattamento con Bosentan Sandoz ha inizio normalmente con l'assunzione di 2 mg per kg di peso corporeo due volte al giorno (mattina e sera). Tuttavia, alcune dosi di bosentan non sono adatte nei bambini con un peso corporeo inferiore a 31 kg. Per questi pazienti è necessaria una compressa di bosentan con dosaggio minore. Il dosaggio verrà definito dal medico.
Bosentan è disponibile anche in forma di compresse dispersibili da 32 mg, che possono facilitare il corretto dosaggio nei bambini e nei pazienti con basso peso corporeo o con difficoltà a deglutire le compresse rivestite con film.
Se lei ha l'impressione che gli effetti di Bosentan Sandoz siano troppo forti o troppo deboli, parli con il medico allo scopo di valutare se è necessario cambiare la posologia.

Come prendere Bosentan Sandoz
Assumere le compresse (mattina e sera) deglutendole con acqua. Le compresse possono essere assunte a digiuno o a stomaco pieno.

Se prende più Bosentan Sandoz di quanto deve
Se prende più compresse di quante prescritte, consulti immediatamente il medico.

Se dimentica di prendere Bosentan Sandoz
Se dimentica di assumere Bosentan Sandoz, prenda una compressa non appena si ricorda e poi continui ad assumere le compresse agli orari abituali. Non prenda una dose doppia per compensare la dimenticanza di una compressa.

Se interrompe il trattamento con Bosentan Sandoz
La sospensione improvviso del trattamento con Bosentan Sandoz può comportare un aggravamento dei sintomi. Non sospenda il trattamento con Bosentan Sandoz se non su indicazione del medico. Il medico può consigliarle di ridurre la dose nell'arco di alcuni giorni prima di sospendere definitivamente il trattamento con Bosentan Sandoz.

Se ha qualsiasi dubbio sull'uso di questo medicinale, si rivolga al medico o al farmacista.

4. Possibili effetti indesiderati

Come tutti i medicinali, questo medicinale può causare effetti indesiderati sebbene non tutte le persone li manifestino.

Gli effetti indesiderati più gravi connessi a Bosentan Sandoz sono:
- Alterazione della funzione del fegato che può interessare più di 1 persona su 10
- Anemia (riduzione dei valori negli esami del sangue) che può interessare fino a 1 persona su 10. L'anemia, occasionalmente, può necessitare di una trasfusione di sangue

I valori risultanti dagli esami del fegato e del sangue devono essere monitorati durante il trattamento con Bosentan Sandoz (vedere paragrafo 2). E' importante che lei faccia questi controlli così come prescritto dal medico.

I segni di un non corretto funzionamento del fegato includono:
- nausea (impulso a vomitare)
- vomito
- febbre (temperatura elevata)
- dolori allo stomaco (addome)
- ittero (ingiallimento della pelle o della parte bianca dell'occhio)
- urina di colore scuro
- prurito della pelle

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- letargia o affaticamento (stanchezza o spossatezza insuali)
- sindrome simil-influenzale (dolori alle articolazioni e ai muscoli con febbre)

Se nota la comparsa di uno di questi segni **informi immediatamente il medico.**

Altri effetti indesiderati:

Molto comuni (possono interessare **più di 1 persona su 10**):
- Mal di testa
- Edema (gonfiore delle gambe e delle caviglie o altri segni dovuti a ritenzione dei liquidi)

Comuni (possono interessare **fino a 1 persona su 10**):
- Aspetto arrossato o arrossamento della pelle
- Reazioni di ipersensibilità (che includono infiammazione della pelle, prurito e eruzione cutanea)
- Malattia da reflusso gastroesofageo (reflusso acido)
- Diarrea
- Sincope (svenimento)
- Palpitazioni (battiti del cuore veloci o irregolari)
- Pressione sanguigna bassa
- Congestione nasale

Non comuni (possono interessare **fino a 1 persona su 100**):
- Trombocitopenia (basso numero di piastrine nel sangue)
- Neutropenia/leucopenia (basso numero di globuli bianchi)
- Alterazioni negli esami di funzionalità epatica associate a epatite (infiammazione del fegato) inclusa possibile esacerbazione dell'epatite esistente e/o ittero (ingiallimento della cute o della parte bianca dell'occhio)

Rari (possono interessare **fino a 1 persona su 1000**):
- Anafilassi (reazione allergica generalizzata), angioedema (gonfiore, più comune intorno ad occhi, labbra, lingua o gola)
- Cirrosi (cicatrizzazione) del fegato, insufficienza epatica grave (grave disturbo della funzionalità del fegato)

È stato segnalato anche offuscamento della vista con una frequenza non nota (la frequenza non può essere definita sulla base dei dati disponibili).

Effetti indesiderati aggiuntivi nei bambini e adolescenti
Gli effetti indesiderati che sono stati riportati nei bambini trattati con Bosentan Sandoz sono gli stessi di quelli degli adulti.

Segnalazione degli effetti indesiderati
Se manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio, si rivolga al medico o al farmacista. Lei può inoltre segnalare gli effetti indesiderati direttamente tramite il sistema nazionale di segnalazione all'indirizzo www.aifa.gov.it/content/segnalazioni-reazioni-avverse. Segnalando gli effetti indesiderati lei può contribuire a fornire maggiori informazioni sulla sicurezza di questo medicinale.

5. Come conservare Bosentan Sandoz

Conservi questo medicinale fuori dalla vista e dalla portata dei bambini.

Non usi questo medicinale dopo la data di scadenza che è riportata sulla scatola e sul blister dopo Scad. La data di scadenza si riferisce all'ultimo giorno di quel mese.

Questo medicinale non richiede alcuna condizione particolare di conservazione.

Non getti alcun medicinale nell'acqua di scarico e nei rifiuti domestici. Chieda al farmacista come eliminare i medicinali che non utilizza più. Questo aiuterà a proteggere l'ambiente.

6. Contenuto della confezione e altre informazioni

Cosa contiene Bosentan Sandoz

Bosentan Sandoz 62,5 mg compresse rivestite con film: Il principio attivo è il bosentan (come monoidrato).

Ogni compressa contiene 62,5 mg di bosentan (corrispondenti a 64,541 mg di bosentan monoidrato).

Bosentan Sandoz 125 mg compresse rivestite con film: Il principio attivo è il bosentan (come monoidrato).

Ogni compressa contiene 125 mg di bosentan (corrispondenti a 129,082 mg di bosentan monoidrato).

Gli altri componenti all'interno della compressa sono: amido di mais, amido di mais pregelatinizzato, sodio amido glicolato tipo A, povidone K30, poloxamer 188, silice colloidale anidra, glicerolo dibenoato e magnesio stearato.

Il rivestimento in film contiene Opadry Orange 21K23007 (contenente ipromellosa, titanio diossido, eticellulosa, triacetina, talco, ferro ossido giallo (E172), ferro ossido rosso (E172), ferro ossido nero (E172).

Descrizione dell'aspetto di Bosentan Sandoz e contenuto della confezione

Bosentan Sandoz 62,5 mg compresse rivestite con film sono compresse rivestite con film di colore arancione chiaro, rotonde, biconvesse di 6 mm di diametro

Bosentan Sandoz 125 mg compresse rivestite con film sono compresse rivestite con film di colore arancione chiaro, ovali, biconvesse di dimensioni 11 mm x 5 mm.

Blister: PVC/PVDC/Alluminio contenenti 14 compresse rivestite con film.

Le scatole contengono 14, 56 o 112 compresse rivestite con film

E' possibile che non tutte le confezioni siano commercializzate.

Titolare dell'autorizzazione all'immissione in commercio

Sandoz S.p.A.
L.go U. Boccioni 1, 21040 Origgio (VA)
Italia

Produttore

GE Pharmaceuticals Ltd.
Industrial Zone, 'Chekantzo-South' area, Botevgrad 2140
Bulgaria

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana
Slovenia

Questo medicinale è autorizzato negli Stati Membri della Spazio Economico Europeo con le seguenti denominazioni:

Paesi Bassi	Bosentan Sandoz 62,5 mg, filmomhulde tabletten Bosentan Sandoz 125 mg, filmomhulde tabletten
Austria	Bosentan Sandoz 62.5 mg, Filmtabletten Bosentan Sandoz 125 mg, Filmtabletten
Belgio	Bosentan Sandoz 62.5 mg, filmomhulde tabletten Bosentan Sandoz 125 mg, filmomhulde tabletten
Bulgaria	Bosentan Sandoz 62.5 mg филмирана таблетка Bosentan Sandoz 125 mg филмирана таблетка
Repubblica Ceca	Bosentan Ebewe
Germania	Bosentan HEXAL 62.5 mg, Filmtabletten Bosentan HEXAL 125 mg, Filmtabletten
Spagna	Bosentan Sandoz Farmaceutico 62.5 mg, comprimidos recubiertos con película EFG Bosentan Sandoz Farmaceutico 125 mg, comprimidos recubiertos con película EFG
Finlandia	Bosentan Sandoz 62.5 mg, tabletti, kalvopäällysteinen Bosentan Sandoz 125 mg, tabletti, kalvopäällysteinen
Francia	BOSENTAN SANDOZ 62.5 mg, comprimé pelliculé BOSENTAN SANDOZ 125 mg, comprimé pelliculé
Italia	Bosentan Sandoz
Lettonia	Bosentan Welding 62.5 mg, apvalkotās tabletes Bosentan Welding 125 mg, apvalkotās tabletes
Norvegia	Bosentan Sandoz 62.5 mg, tablett, filmdrasjert Bosentan Sandoz 125 mg, tablett, filmdrasjert
Polonia	Bosentan Sandoz Gmbh 62,5 mg tabletki powlekane Bosentan Sandoz Gmbh 125 mg tabletki powlekane
Portogallo	Bosentano Sandoz
Romania	Bosentan Sandoz 62.5 mg, comprimate filmate Bosentan Sandoz 125 mg, comprimate filmate
Svezia	Bosentan Sandoz 62.5 mg, filmdragerad tablett Bosentan Sandoz 125 mg, filmdragerad tablett
Slovacchia	Bosentan Sandoz 62,5 mg Bosentan Sandoz 125 mg

Questo foglio illustrativo è stato aggiornato il 03/2018

CARTA INFORMATIVA DEL PAZIENTE

Informazioni Importanti sulla Sicurezza per i Pazienti che assumono Bosentan Sandoz

Questa scheda contiene informazioni importanti su Bosentan Sandoz. Legga questa scheda attentamente prima di iniziare il trattamento con bosentan.

Nome: _____
Medico prescrittore: _____
Rivolgersi al medico in caso si abbiano domande relative a Bosentan Sandoz.

Sandoz S.p.A.

Se lei è una donna in età fertile, legga questa pagina con attenzione

Gravidanza

Bosentan Sandoz può danneggiare lo sviluppo del feto. Quindi lei non deve assumere Bosentan Sandoz se è in gravidanza e non deve iniziare una gravidanza mentre assume Bosentan Sandoz.

Inoltre, se lei soffre di ipertensione polmonare, la gravidanza può aggravare severamente i sintomi della malattia. Se lei sospetta di poter essere in gravidanza, lo dica al suo medico o ginecologo.

Contraccezione

La contraccezione di tipo ormonale - come i contraccettivi orali o pillole contraccettive, ormoni iniettabili, impianti o cerotti cutanei contraccettivi, non prevengono in maniera affidabile la gravidanza nelle donne che assumono Bosentan Sandoz. Lei ha bisogno di usare un metodo di barriera contraccettiva – come il preliatrico, il diaframma o la spugna vaginale – in aggiunta a ciascuno di questi tipi di contraccettivi ormonali. Si assicuri di discutere ogni possibile domanda con il suo medico o con il ginecologo – compileri i dati richiesti sul retro di questo schedo e la porti al suo medico o ginecologo alla prossima visita.

Lei deve effettuare un test di gravidanza prima di iniziare Bosentan Sandoz e ogni mese durante il trattamento anche se pensa di non essere in gravidanza.

Data del primo test mensile: _____

Contraccezione

Lei abitualmente prende o usa contraccettivi?
☐ Sì ☐ No

Se sì, scriva i loro nomi qui:
_____
_____

Porti questa scheda al suo medico o ginecologo alla prossima visita e lui/lei sarà in grado di consigliarla sulla necessità di usare metodi contraccettivi addizionali o alternativi.

Analisi del sangue per la funzione epatica

È stato riscontrato che alcuni pazienti sottoposti al trattamento con Bosentan Sandoz presentavano esiti anomali negli esami per la funzionalità epatica. Durante il trattamento con Bosentan Sandoz il medico provvederà a richiedere esami del sangue al fine di controllare con regolarità eventuali cambiamenti della funzionalità epatica.

Si ricordi di fare ogni mese l'esame del sangue per la funzionalità epatica. A seguito di un aumento della dose, verrà effettuato un esame addizionale dopo 2 settimane.

Data del primo esame mensile: _____

Il suo programma mensile di analisi del sangue per il fegato:

☐ Gen	☐ Mag	☐ Set
☐ Feb	☐ Giu	☐ Ott
☐ Mar	☐ Lug	☐ Nov
☐ Apr	☐ Ago	☐ Dic

Інструкція: інформація для користувача

-логотип Сандоз-

Бозентан-Сандоз 62,5 мг таблетки, вкриті плівкою оболонкою
Бозентан-Сандоз 125 мг таблетки, вкриті плівкою оболонкою

Лікарський засіб - генерик

Уважно прочитайте цей вкладиш, перш ніж розпочати прийом препарату, оскільки він містить важливу для Вас інформацію.

- Зберігайте цей вкладиш. Можливо Вам буде необхідно перечитати його знову.
- Якщо у Вас виникнуть будь-які сумніви, будь ласка, зверніться до Вашого лікаря або фармацевта.
- Цей препарат був призначений особисто Вам. Не передавайте його іншим особам, навіть якщо вони мають такі ж симптоми, як у Вас, оскільки це може бути небезпечно для них.
- Якщо Ви помітили бідь-які побічні реакції, навіть такі, що не зазначені у цьому вкладиші, зверніться до свого лікаря або фармацевта. Дивіться параграф 4.

Вміст цього вкладишу:

1. Що таке Бозентан-Сандоз і для чого він застосовується.

Таблетки Бозентан-Сандоз містять бозентан, який блокує присутній у натуральному вигляді в організмі гормон, який називається ендотелін-1 (ЕТ-1), що причиняє звуження кровоносних судин. Отже, Бозентан-Сандоз викликає розширення судин та належить до класу лікувальних засобів, які називаються «антагоністами рецепторів ендотеліну».

Бозентан-Сандоз використовується для лікування:

- **Легеневої артеріальної гіпертензії (ЛАГ)**. ЛАГ – це захворювання, викликане значним звуженням кровоносних судин легенів, внаслідок чого у кровоносних судинах, які переносять кров від серця до легенів (легеневих артеріях), збільшується тиск. Цей тиск зменшує кількість кисню, який може поступити у кров через легені, що утруднює фізичну діяльність. Бозентан-Сандоз розширює легеневі артерії, що допомагає серцю нагнітати в них кров, а це приводить до зменшення кров'яного тиску та послаблення симптомів захворювання.

Бозентан-Сандоз застосовується при лікуванні хворих на легеневу артеріальну гіпертензію (ЛАГ) III функціонального класу для покращення здатності здійснювати фізичну діяльність та

полегшення симптомів захворювання. «Функціональний клас» означає рівень тяжкості хвороби: «III функціональний клас» характеризується вираженим обмеженням фізичної діяльності. Деякі поліпшення були виявлені також у пацієнтів з ЛАГ II функціонального класу. «II функціональний клас» має менші обмеження у здійсненні фізичної діяльності. Бозентан-Сандоз може призначатися для наступних видів ЛАГ:

- первинна (без ідентифікованої причини або сімейного анамнезу);
- викликана склеродермією (інша назва: системний склероз – хвороба, що супроводжується аномальним ростом сполучної тканини, яка підтримує шкіру та інші органи);
- викликана вродженими вадами серця з шунтом (аномальні провідні шляхи), які визначають анормальний кров'яний потік через серце та легені.

- **Виразки на пальцях** (пошкодження пальців рук та ніг): у дорослих пацієнтів з захворюванням, яке називається склеродермія. Бозентан-Сандоз зменшує кількість нових виразок на пальцях рук та ніг.

2. Що треба знати перед початком прийому Бозентан-Сандоз.

Не приймайте Бозентан-Сандоз:

- **якщо у Вас алергія на бозентан** або на будь-яку іншу допоміжну речовину цього препарату (перелік у параграфі 6);
- **якщо у Вас є порушення функції печінки** (проконсультуйтеся у лікаря);
- **якщо Ви вагітна або можете завагітніти**, оскільки не користуєтесь надійними методами контрацепції. Будь ласка, уважно прочитайте інформацію, наведену у статтях «Контрацептиви» та «Інші лікарські засоби та Бозентан-Сандоз»;
- **якщо Ви приймаєте циклоспорин А** (лікарський засіб, який використовується після пересадки органів або для лікування псоріазу).

Проконсультуйтеся у лікаря, якщо один з перелічених вище станів Вас стосується.

Застережні заходи та рекомендації

Проконсультуйтеся у лікаря або фармацевта перед початком прийому Бозентан-Сандоз.

Аналізи, які призначить лікар перед початком лікування:

- аналіз крові для перевірки функції печінки;
- аналіз крові для виявлення наявності анемії (низького рівню гемоглобіну);
- тест на вагітність (для жінок дітородного віку).

У деяких пацієнтів, які проходять курс лікування препаратом Бозентан-Сандоз, були виявлені аномальні результати аналізів на функцію печінки та анемію (низький гемоглобін).

БОГОЛЄПОВ А.А.

Аналізи, які призначить лікар під час лікування

Під час лікування препаратом Бозентан-Сандоз лікар буде регулярно призначати Вам аналізи крові з метою моніторингу змін у функції печінки та рівні гемоглобіну.
Для проведення аналізів посилатися також на Пам'ятку для пацієнта (що міститься в упаковці Бозентан-Сандоз). Важливо регулярно проходити такі аналізи крові протягом усього періоду прийому препарату Бозентан-Сандоз. Рекомендується записувати в Пам'ятці для пацієнта дату проведення останнього аналізу, а також дату проведення наступного запланованого аналізу (запитайте дату у лікаря). Це допоможе Вам не забути, коли необхідно зробити наступний аналіз.

Аналіз крові на функцію печінки (печінкова проба)
Проводиться щомісячно протягом усього періоду лікування Бозентан-Сандоз. Вам буде призначено додатковий аналіз через 2 тижня після збільшення дози.

Аналіз крові на анемію

Проводиться щомісячно протягом перших 4 місяців лікування, потім один раз на 3 місяці, оскільки у пацієнтів, які приймають Бозентан-Сандоз, може розвинутися анемія.
У випадку аномалій в результатах аналізів, лікар може вирішити зменшити дозу або перервати лікування препаратом Бозентан-Сандоз та провести додаткові аналізи для виявлення причини.

Діти та підлітки

Бозентан-Сандоз не рекомендований для прийому педіатричними пацієнтами з активними виразками на пальцях та систематичним склерозом. Бозентан-Сандоз не повинен прийматися дітьми хворими на легеневу артеріальну гіпертензію, які мають вагу тіла меншу за 31 кг. Дивіться також параграф 3 «Як приймати Бозентан-Сандоз».

Інші лікарські засоби та Бозентан-Сандоз
Поінформуйте лікаря або фармацевта, якщо ви приймаєте, приймали нещодавно або плануєте прийом інших лікарських засобів, в тому числі препаратів, отриманих без призначення лікаря.
Особливо важливо повідомити лікаря про прийом таких препаратів:

- циклоспорин А (лікарський засіб, який використовується після пересадки органів або для лікування псоріазу), який не повинен прийматися разом в Бозентан-Сандоз;
- сіролімус або такролімус – лікарські засоби, які використовуються після пересадки органів; їх прийом разом з Бозентан-Сандоз не рекомендований.

БОГОЛЄПОВ А.А.

БЮРО ПЕРЕКЛАДІВ

- глібенкламід (препарат для лікування діабету), ріфампіцин (препарат для лікування туберкульозу), флюконазол або кетоконазрол (препарати для лікування грибкових інфекцій), невірапін (препарат для лікування ВІЛ-інфекції), оскільки прийом цих лікарських засобів разом з Бозентан-Сандоз не рекомендований;
- інші лікарські засоби для лікування ВІЛ-інфекції, які можуть вимагати особливий нагляд, якщо приймаються разом з Бозентан-Сандоз.
- гормональні контрацептиви, які не є ефективними в якості єдиного контрацептивного засобу під час прийому Бозентан-Сандоз. Всередині упаковки Бозентан-Сандоз Ви знайдете Пам'ятку для пацієнта, яку потрібно уважно прочитати. Лікар та/або гінеколог визначать метод контрацептивного захисту, підходящий для Вас;
- інші лікарські засоби для лікування легеневої гіпертензії: силденафіл та таданафіл;
- варфарин (антикоагулянт);
- сімвастатин (застосовується при лікуванні гіперколестерололемії).

Бозентан-Сандоз з їжею та напоями
Бозентан-Сандоз можна приймати натще або на повний шлунок.

Вагітність, годування груддю та фертильність
Якщо Ви вагітна, підозрюєте або плануєте вагітність або якщо кормите груддю, перед початком прийому цього лікарського засобу проконсультуйтеся у лікаря або фармацевта.

Жінки дітородного віку
НЕ приймайте Бозентан-Сандоз, якщо ви вагітна або намагаєтесь завагітніти.

Тест на вагітність
Бозентан-Сандоз може нашкодити очікуваній дитині, зачатій перед або під час лікування цим препаратом. Якщо Ви є жінкою дітородного віку, лікар попросить Вас зробити тест на вагітність перед початком прийому Бозентан-Сандоз і потім повторювати його регулярно протягом курсу лікування цим лікарським засобом.

Контрацептиви
Якщо ви є жінкою дітородного віку, користуйтеся надійним методом контролю дітородіння (контрацептивом) під час прийому Бозентан-Сандоз. Лікар або гінеколог порадить Вам контрацептивні засоби, які будуть надійними протягом лікування препаратом Бозентан-Сандоз. Оскільки Бозентан-Сандоз може нейтралізувати дію гормональних контрацептивів (наприклад, оральних, ін'єкційних, імплантованих контрацептивів або трансдермальних пластирів), такий метод самий собою не є ефективним. Отже, якщо Ви користуєтеся гормональними контрацептивами, Ви повинні застосовувати також бар'єрні методи (наприклад, жіночий презерватив, діафрагму, контрацептивну губку або Ваш партнер також повинен використовувати

БОГОЛЄПОВ А.А.

Україна БЮРО ПЕРЕКЛАДІВ

презерватив). Всередині упаковки Бозентан-Сандоз Ви знайдете Пам'ятку для пацієнта. Ви повинні заповнити цю Пам'ятку та показати її вашому лікарю під час наступного візиту, таким чином лікар або гінеколог зможуть дати висновок, чи маєте Ви потребу у додаткових або альтернативних надійних методах контрацепції. Якщо Ви дітородного віку, під час прийому Бозентан-Сандоз рекомендовано виконувати тест на вагітність щомісячно.

Негайно повідомте лікарю, якщо почнеться вагітність під час прийому Бозентан-Сандоз або якщо Ви маєте намір завагітніти у найближчий час.

Лактація

Негайно **повідомте лікарю, якщо ви кормите груддю**. Рекомендовано перервати кормління груддю, у випадку якщо Вам буде прописаний Бозентан-Сандоз, оскільки не відомо, чи цей лікарський засіб виділяється з грудним молоком.

Фертильність

Якщо ви - чоловік, який приймає Бозентан-Сандоз, є можливість, що цей препарат зменшить кількість сперматозоїдів. Неможна виключити, що це зменшить можливість зачаття дитини. Проконсультуйтеся у лікаря, якщо у Вас є питання.

Керування транспортними засобами та користування механізмами

Бозентан-Сандоз може привести до гипотензії (зменшення кров'яного тиску), що може викликати запаморочення, вплинути на Ваш зір та здатність керувати транспортним засобом та користуватися механізмами. Отже, якщо Ви відчуваєте запаморочення голови або затуманення зору під час прийому Бозентан-Сандоз, не керуйте транспортними засобами та не користуйтеся будь-якими інструментами чи механізмами.

3. Як приймати Бозентан-Сандоз

Вживайте цей лікарський засіб, точно дотримуючись інструкцій лікаря чи фармацевта. Якщо у Вас виникнуть сумніви, проконсультуйтеся у лікаря чи фармацевта.

Лікування препаратом Бозентан-Сандоз повинне розпочинатися тільки з ініціативи лікаря, який має досвід у лікуванні ЛАГ або системного склерозу, та під його наглядом.

Рекомендована доза

Дорослі

У дорослих лікування в нормі починається з прийому однієї таблетки по 62,5 мг 2 рази на день (вранці та ввечері) протягом перших чотирьох тижнів, потім лікар зазвичай порадить Вам

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приймати одну таблетку по 125 мг 2 рази в день в залежності від виявленої відповіді на препарат Бозентан-Сандоз.

Діти та підлітки

Рекомендована доза для дітей призначена тільки для ЛАГ. Для дітей віком 1 рік та більше лікування препаратом Бозентан-Сандоз розпочинається зазвичай з вживання 2 мг на 1 кг ваги тіла 2 рази на день (вранці та ввечері). Однак деякі дози бозентану є непридатними для дітей з вагою тіла менше 31 кг. Таким пацієнтам потрібна 1 таблетка бозентану меншої дозировки. Дозировка дня них визначається лікарем.

Існує також бозентан у формі диспергованих таблеток по 32 мг, які можуть спростити вибір правильного дозування у дітей та пацієнтів з низькою вагою тіла або утрудненим заковтуванням таблеток, вкритих плівкою (оболонкою).

Якщо Ви маєте враження, що реакція на вживання Бозентан-Сандоз занадто сильна або занадто слабка, порадьтеся з лікарем, щоб оцінити, чи необхідно змінити дозу.

Як приймати Бозентан-Сандоз

Вживати таблетки (вранці та ввечері), заковтуючи та запиваючи водою. Можна приймати таблетки натще або на повний шлунок.

Якщо Ви вжили більше препарату Бозентан-Сандоз, ніж треба

Якщо Ви випили більше таблеток, ніж було Вам прописано, негайно проконсультуйтеся з лікарем.

Якщо Ви забули прийняти Бозентан-Сандоз

Якщо Ви забули прийняти Бозентан-Сандоз, випийте одну таблетку одразу, як Ви згадали, а потім продовжуйте вживати таблетки за звичайним розкладом. Не приймайте подвійну дозу, щоб компенсувати таблетку, яку Ви пропустили.

Якщо Ви перервали лікування препаратом Бозентан-Сандоз

Раптове припинення лікування препаратом Бозентан-Сандоз може привести до погіршення симптомів. Ви можете перервати лікування препаратом Бозентан-Сандоз тільки за показаннями лікаря. Лікар може порекомендувати Вам зменшувати дозу протягом кількох днів перед тим, як остаточно припинити лікування препаратом Бозентан-Сандоз.

Якщо у Вас виникнуть будь-які сумніви щодо вживання цього лікарського засобу, зверніться до лікаря або фармацевта.

4. Можливі побічні реакції

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Як і будь-які інші лікарські засоби, цей препарат може викликати побічні реакції, хоча не в усіх людей вони виникають.

Найважчими побічними реакціями, пов'язаними з препаратом Бозентан-Сандоз, є:

- Альтерація функції печінки, яка може стосуватися більше 1 особи з 10;
- Анемія (зниження показників в аналізах крові), яка може стосуватися до 1 особи з 10. Іноді при анемії може виникнути потреба у переливанні крові.

Результати аналізів крові та печінкових проб повинні моніторуватися протягом лікування лікарським засобом Бозентан-Сандоз (див. параграф 2). Важливо, щоб Ви проходили ці перевірки так, як це прописано лікарем.

До ознак неправильної роботи печінки входять:

- нудота (позив до блювання);
- блювота;
- жар (висока температура);
- біль у шлунку (животі);
- жовтуха (пожовтіння шкіри та білої частини ока);
- сеча темного кольору;
- свербіж шкіри;
- летаргія або обтяження (незвичайні стомленість або знесилення);
- грипоподібний синдром (болі у суглобах та м'язах з жаром).

Якщо помітите появу одного з цих ознак **негайно повідомте про це лікарю**.

<u>Інші побічні реакції:</u>

Дуже розповсюджені (можуть стосуватися **більше 1 особи з 10**):

- головний біль;
- набряк (напухання ніг та щиколоток або інші ознаки утримання рідини).

Розповсюджені (можуть стосуватися **до 1 особи з 10**):

- почервонілий вигляд шкіри або її почервоніння;
- реакції гіперчутливості (в тому числі запалення шкіри, свербіж, шкірний висип);
- синдром шлунково-стравохідного рефлюксу (кислий рефлюкс);
- діарея;
- синкопе (непритомність);
- пальпітація (посилене та нерегулярне биття серця);
- низький кров'яний тиск;
- закладення носа.

Нерозповсюджені (можуть стосуватися **до 1 особи зі 100**):

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- тромбоцитопенія (низький рівень тромбоцитів у крові);
- нейтропенія / лейкопенія (низький рівень лейкоцитів);
- відхилення в печінкових пробах, пов'язані з гепатитом (запаленням печінки), в тому числі можливе загострення симптомів наявного гепатиту та/або жовтуха (пожовтіння шкіри або білої частини ока).

Рідкі (можуть стосуватися **до 1 особи зі 1000**):

- анафілаксія (загальна алергічна реакція), ангіоедема (набряки, найчастіше навколо очей, губ, язика чи горла);
- цироз (рубцювання) печінки, важка печінкова недостатність (важке захворювання функції печінки).

Існують також повідомлення про затуманення зору, частота виникнення якого невідома (частота не може бути визначена на підставі наявних даних).

Додаткові побічні реакції у дітей та підлітків
Побічні реакції, що були виявлені у дітей при прийомі Бозентан-Сандоз, ті самі, що й у дорослих.

Повідомлення про побічну реакцію
Якщо з'являється будь-яка небажана реакція, в тому числі така, що неперелічена у цьому вкладиші, зверніться до лікаря або фармацевта. Ви можете надіслати повідомлення про побічні реакції безпосередньо в італійську національну систему повідомлення через інтернет-сайт: www.aifa.gov.it/content/segnalazioni-reazioni-avverse. Повідомляючи про небажані реакції, Ви робите внесок у поповнення інформації про безпечність цього лікарського засобу.

5. Як зберігати Бозентан-Сандоз

Зберігати у недоступному для дітей місці.

Не вживайте цей лікарський засіб після закінчення його терміну придатності, зазначеного на коробці та на блістері після слів «Термін придатності». Під терміном придатності розуміється останній день зазначеного місяця.

Цей лікарський засіб не потребує спеціальних умов зберігання.

Не викидайте лікарські засоби у стічні води та у домашнє сміття. Запитайте у фармацевта, як позбутися лікарських засобів, якими Ви більше не користуєтеся. Це допоможе захистити навколишнє середовище.

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ЛІНГО * м. Київ * Україна * Товариство з обмеженою відповідальністю * БЮРО ПЕРЕКЛАДІВ